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A Review on Recent Syntheses of Amaryllidaceae Alkaloids and Isocarbostyrils (Time period mid-2016 to 2017)

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Alkaloids from the Amaryllidaceae have become valuable targets for synthetic organic chemists, mainly due to their wide variety of bioactivities and potential for utilization in medicinal chemistry ventures. In addition, the structural complexity of a number of these alkaloids has also been a reason for the interest in these compounds. In this review, the last 18 months of literature was perused and synthetic highlights have been presented here, with the hope to further focus attention on this interesting class of compounds and to encourage others to synthesize these compounds and their derivatives and/or analogues. The review contains examples of syntheses from most of the important alkaloid scaffold classes previously isolated from the Amaryllidaceae, namely: lycorine, crinine, galanthamine, tazettine, montanine, phenanthridone, phenanthridine, plicamine, mesembrine and some minor scaffolds (like gracilamine).

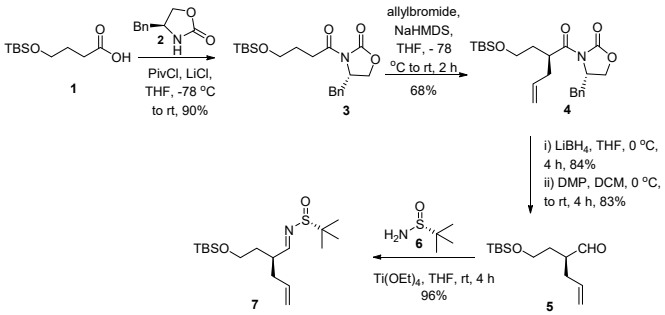
Keywords: Amaryllidaceae, Alkaloids, Isocarbostyrils, Synthesis, Lycorine, Crinine, Galanthamine, Tazettine, Montanine, Phenanthridone, Phenanthridine, Plicamine, Mesembrine, Gracilamine.

The aim of this review is to present new syntheses of Amaryllidaceae alkaloids [1] published during the late period of 2016 to October 2017. This has been done to supplement and extend two recent excellent reviews, namely by Hudlicky and co-workers [2] and Jin [3], both of which extensively focus on synthetic progress in this field. In addition, other topical recent reviews on various important aspects of the Amaryllidaceae alkaloids, exemplified by Kornienko and Evidente [1a], He *et al.* [1b], Nair *et al*. [1c-e], Ding and co-workers [4], Evidente and co-workers [5] and Hotchandani and Desgagne-Penix [6] serve as testimony to the tremendous growing interest by synthetic and natural product chemists in the biological value these alkaloids possess. Our information is derived from the very latest articles we were able to source from our search engines. It should be noted that the focus will be on total and formal syntheses and not specifically on advances in enzyme-mediated approaches [7-9], in-silico-based research [10] or natural product isolation as for instance in these recent literature examples [11-13].

The syntheses are arranged and presented in such a way as to represent, as far as possible, similar classes of the Amaryllidaceae alkaloids, as utilized in recent reviews [4]. However, there could be a degree of overlap due to the very nature of the various syntheses since a particular synthetic intermediate might be a useful synthon for a number of different members of this alkaloid family. It should also be noted that, on occasion, some finer details might have been omitted from reaction schemes and these can easily be obtained from the references. We trust that our overview of these 18 months will provide evidence of the intense synthetic focus on the Amaryllidaceae alkaloids and will thus enthuse more researchers to participate in generating these compounds, their analogues and derivatives.

a) Lycorine-scaffold alkaloids:

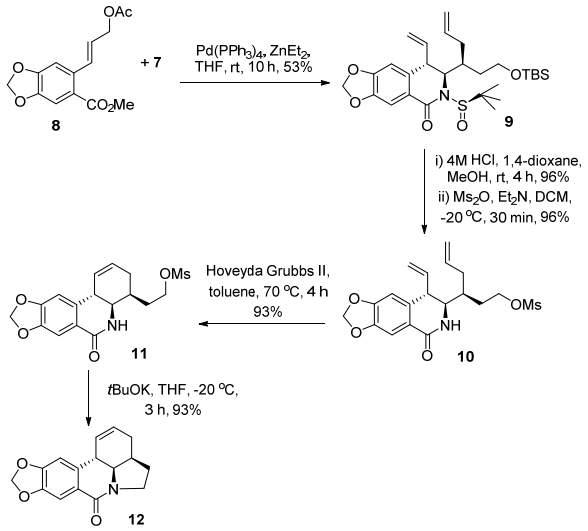
i) Asymmetric total syntheses of (-)-lycorane, (-)-zephyranthine, and a formal synthesis of (+)-clivonine, by Sun and co-workers: Sun and co-workers developed a fairly rapid protocol for the synthesis of another pivotal intermediate **11**, based on their earlier work [14], which acted as a most innovative scaffold for its further transformation into a number of Amaryllidaceae alkaloids [15]. Thus, starting from the TBS-protected 4-hydroxy butanoic acid **1**, Evan's auxiliary **2** was easily and efficiently introduced to give the chiral intermediate **3** (90%). This was followed by an asymmetric α-allylation on the carbonyl alkyl chain to produce **4** (68%) with a d.r. >20:1. Removal of the chiral auxiliary with $LiBH_4$, followed by Dess-Martin periodane-mediated oxidation of the corresponding primary alcohol provided aldehyde **5** (70% for the 2 steps), which was converted into the one very important intermediate viz., **7** (96%) by treatment with (*R*)-*N*-*tert*-butanesulfinyl amine **6** in the presence of $Ti(OEt)_4$ (Scheme 1).



Scheme 1: Synthesis of sulfinyl amine **7**.

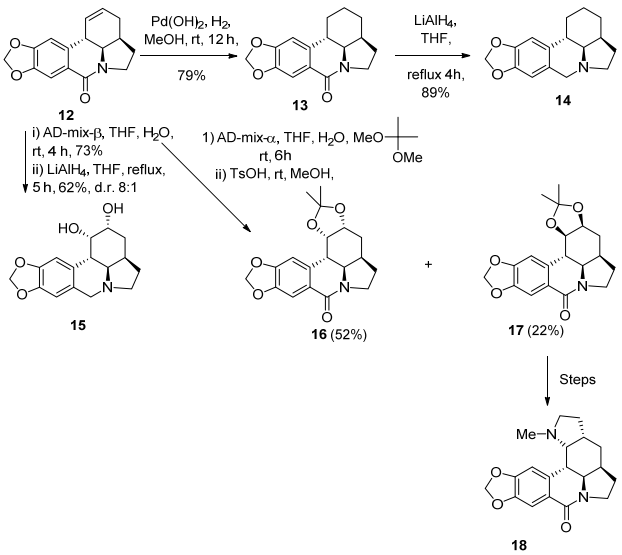
Reaction between the building blocks **7** and **8** under palladium-catalysed cinnamylation conditions, followed by a spontaneous cyclization afforded the stereospecifically desired product **9** (53%) (d.r. >20:1). As noted, this protocol generated two consecutive stereocentres, in addition to ring B in a 1-pot sequence. Removal of both protecting groups under acidic conditions then gave a lactam alcohol (96%) which was re-protected as the mesylate **10** (96%) by reaction with methane sulfonic anhydride (Scheme 2). A subsequent

RCM using Hoveyda-Grubbs II generation catalyst caused the precipitation of the product **11** (93%) which was now set up for formation of ring D and was achieved by using the relatively weaker and bulkier base *t*BuOK (cf NaH) to prevent any possible racemization, to form the pivotal intermediate **12** (Scheme 2).



Scheme 2: Synthesis of pivotal intermediate **12**.

In order to illustrate the value of intermediate **12**, it was converted into three important Amaryllidacae alkaloids illustrated in Scheme 3. Thus $Pd(OH)_2$ catalysed hydrogenation afforded lactone **13** (79%) which upon reduction with $LiAlH_4$ in THF under reflux gave the enantiomerically pure α-lycorane **14** (89%). Alternatively, Sharpless asymmetric dihydroxylation of **12** with AD-mix-β gave the C1, C2 *cis*-diol (73%) with a d.r. = 8:1. Reduction of the lactam with $LiAlH_4$ then afforded zephyranthine **15** (62%). On the other hand, performing the dihydroxylation with AD-mix-α followed by acetonidation lead to isolation of products **16** (52%) and **17** (22%) in which the latter compound was an intermediate in the formal total synthesis of (+)-clivonine **18**.



Scheme 3: Useful conversions of intermediate **12** into α-lycorane **14,** zephyranthine **15** and (+)-clivonine **18**.

ii) Asymmetric total synthesis of (-)-δ-lycorane, by Wei and co-workers: In their asymmetric synthesis of the Amaryllidacae alkaloid (-)-δ-lycorane, Wei and co-workers made good use of a Michael/Michael cascade reaction catalysed by their newly developed chiral squaramide catalyst [16] (Figure 1) in a most efficient way [17].

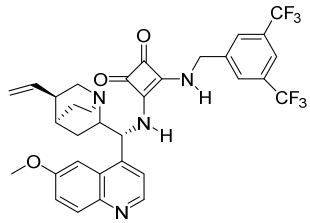
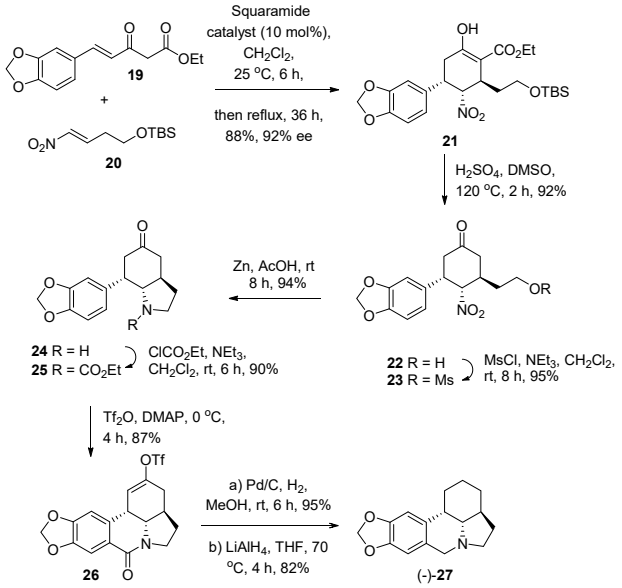


Figure 1: Chiral squaramide catalyst.

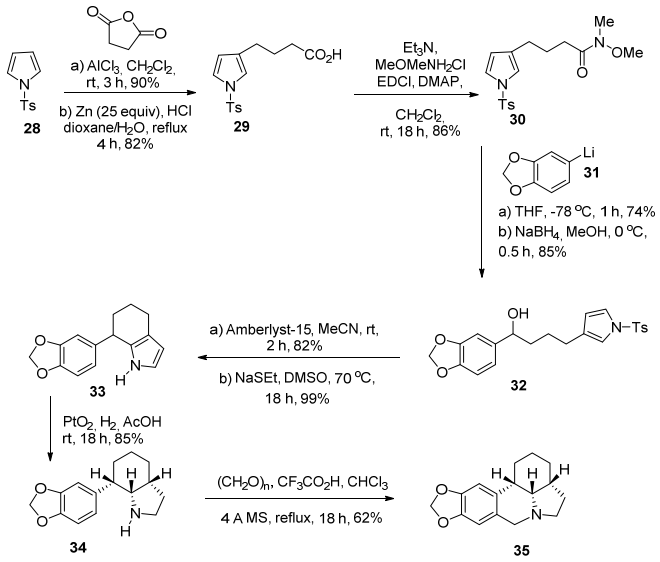
Thus treating ketoester **19** (1 mol) and nitroalkene **20** (1.5 mol) in DCM with 10 mol% of the chiral squaramide catalyst at room temperature for 6 h followed by heating under reflux for 36 h gave an 88% yield of the nitroester **21** with an ee of 92%. This represents an interesting double Michael cascade reaction stereochemically controlled by the catalyst. Treatment of nitroester **21** with dilute H_2SO_4 in DMSO, followed by heating to 120 °C for 2 h lead to the removal of the ester (decarboxylation) and TBS groups to yield alcohol **22** (92%) which was converted into mesylate **23** (95%) under standard conditions. A reductive aminocylisation with zinc powder in acetic acid then afforded the octahydro-indolone **24** (94%), which was then converted into the ethyl carbonate **25** (90%) by reaction with ethyl chloroformate and TEA. The well-established Bischler-Napieralski lactam ring-closure protocol was then efficiently effected with Tf_2O and DMAP in DCM to produce the enol triflate lactam **26** (87%). Palladium-catalysed reduction of the enol triflate afforded the cyclohexane ring (95%) followed by amide reduction with $LiAlH_4$ which then gave the target molecule viz., (-)-δ-lycorane **27** (Scheme 4).



Scheme 4: Enantioselective synthesis of (-)-δ-lycorane **27**.

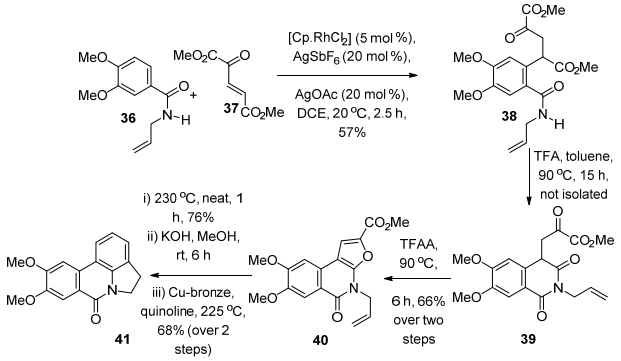
iii) Synthesis of (±)-γ-lycorane by intramolecular Friedel-Crafts reaction, by Bates and co-workers: Bates and co-workers employed an intramolecular Friedel-Crafts reaction to prepare *rac*-γ-lycorane **35** ending with a diastereoselective hydrogenation of a late stage pyrrole intermediate [18]. To this end, *N*-Tosyl pyrrole **28** was subjected to a Friedel-Crafts acylation with succinic anhydride followed by removal of the ketone moiety by Clemmensen

reduction to afford pyrrole **29** (72% for 2 steps). Conversion of the acid **29** into the Weinreb amide **30** was effected by treatment with Et_3N and *N,O*-dimethylhydroxylamine hydrochloride in 86% yield. This intermediate was coupled with the lithiate **31** at -78 °C to give the expected ketone (74%) which was reduced to the corresponding alcohol **32** (86%) with $NaBH_4$ in MeOH at 0 °C. Treatment of the latter alcohol with Amberlyst-15 in MeCN smoothly transformed it into the next Friedel-Crafts product (not illustrated) (82%), and this was immediately followed by detosylation with sodium ethanethiolate to afford pyrrole **33** (99%). Hydrogenation of **33** by the method of Kray and Reinicke using $PtO_2/AcOH/H_2$ under a modest pressure produced **34** as a single stereoisomer. Finally, a Pictet-Spengler reaction with paraformaldehyde in CF_3CO_2H afforded γ-lycorane **35** (62%) (Scheme 5).



Scheme 5: Synthesis of *rac*-γ-lycorane **35**.

iv) Convergent synthesis of oxoassoanine by way of Rh(III)-catalyzed C-H conjugate addition/cyclization reactions, by Weinstein and Ellman: Weinstein and Ellman developed a most useful C-H catalytic addition and cyclisation cascade protocol via a Rh(III) catalyst in their synthesis of the Amaryllidaceae alkaloid, oxoassoanine **41** [19]. Thus, conjugate addition between the *N*-homoallylic benzamide **36** with *trans*-diester **37** in the presence of a Rh(III) catalyst afforded a moderate (57%) yield of the desired product **38** (Scheme 6). Treatment of **38** with TFA afforded imide



Scheme 6: Synthesis of oxoassoanine **41**.

39, which without being isolated, was treated with TFAA. This mediated the Paal-Knorr cyclisation to produce the amidofuran **40** (66% for the 2 steps) in a one pot process. Heating amidofuran **40** neat at 230 °C then gave the Diels-Alder adduct of the tetracyclic system and final decarboxylation with copper-bronze afforded oxoassoanine **41** (68% for the 2 steps).

b) Crinine-scaffold alkaloids

i) Total synthesis of *rac*-joubertiamine and other family members, by Bisai and co-workers: Bisai and co-workers developed a common precursor molecule, *vide infra,* from which they were able to synthesize joubertiamine **42**, mesembrane **43** and crinane **44** scaffolds all of which have structural motif viz., a single all carbon quaternary stereocentre [20] (Figure 2).

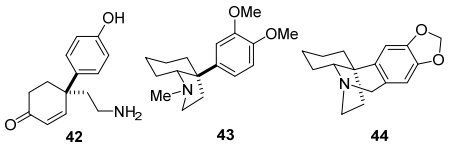
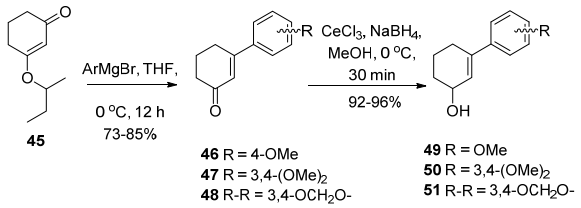
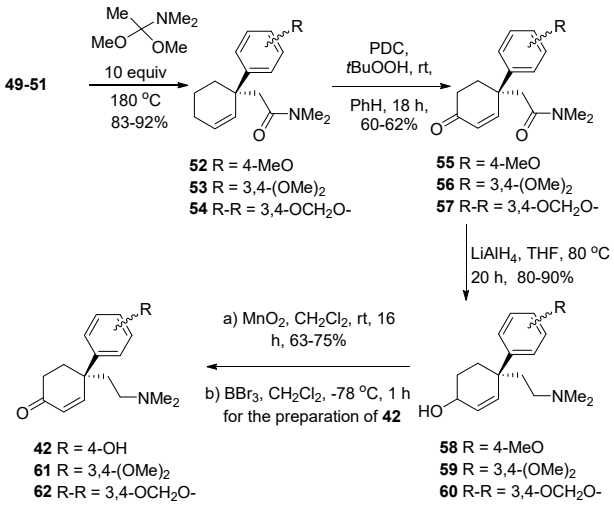


Figure 2: Typical mesembrane-type alkaloids.

Many alkaloids of the Amaryllidaceae family have similar structural motifs and due to their vast biological activity profiles, constitute valuable synthetic challenges. In their new approach, Bisai and co-workers developed a unified strategy to produce a common precursor which would lead to a range of Sceletium and Amaryllidaceae alkaloids [20]. Thus, the Stork-Danheiser protocol was successfully applied to cyclohexenone **45** using appropriate Grignard reagents to produce the corresponding 3-aryl-2-cyclohexenones **46-48**, each of which was reduced by the Luche protocol to afford the corresponding alcohols **49-51** in excellent yields of 92-96% (Scheme 7).



Scheme 7: Synthesis of 3-(aryl)cyclohex-2-enols.

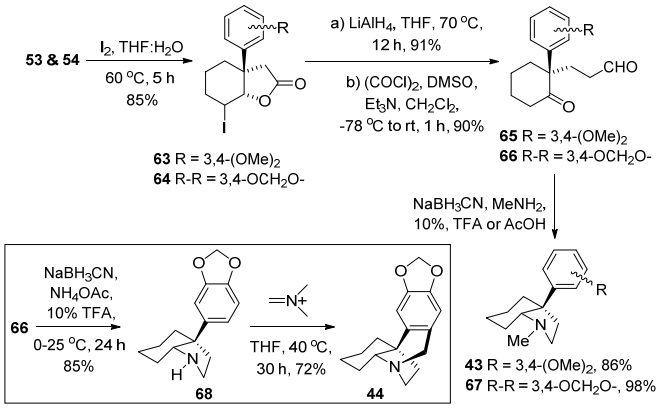


Scheme 8: Formation of joubertiamines.

In order to generate the pivotal quaternary centre, the authors applied the Eschenmoser-Claisen rearrangement on enols **49-51** which produced the desired rearranged amides **52-54** again in

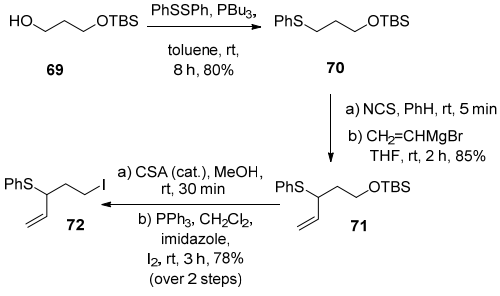
excellent yields of 83-92%. Allylic oxidation with PDC and *tert*-butyl hydroperoxide afforded the enones **55-57** in 60-62% yield. Reduction of the enone amides with $LiAlH_4$ afforded the enol amines **58-60** in yields of 80-90%. Allylic oxidation of the latter enols to the corresponding joubertiamines **61** and **62** was achieved in 67-75% yields. Demethylation of the 4-methoxy precursor to joubertiamine **42** was accomplished by using BBr_3 in DCM at -78 °C for 1 h in an 83% yield (Scheme 8).

In order to employ the pivotal intermediates **53** and **54** for the synthesis of mesembrane and crinane entities, the C2 position was required to be functionalised. To this end, iodolactonization of amides **53** and **54** was performed with I_2 in aqueous THF to afford the iodolactones **63** and **64** in 85% yields respectively. Reduction of these iodolactones with $LiAlH_4$ afforded the deiodated corresponding 1,4-diols in almost quantitative yield which was followed by Swern oxidation to deliver the next key intermediates viz, the ketoaldehydes **65** and **66** in excellent yields of 90% (Scheme 9). The all-important transformation of these latter ketoaldehydes was best effected via a reductive amination using methylamine and sodium cyanoborohydride in ethanol, catalysed by a mixture of either 10% AcOH or 10% TFA to afford the mesembranes **43** and **67** in yields of 86% and 90%, respectively. Finally treatment of ketoaldehyde **66** with ammonium acetate under the standard reductive amination conditions afforded an 85% yield of **68** followed by a rather ingenious usage of Eschenmoser's salt (*N,N*-dimethylmethylene ammonium iodide) to complete the synthesis of crinane **44** (Scheme 9).



Scheme 9: Formation of mesembranes and crinane **44**.

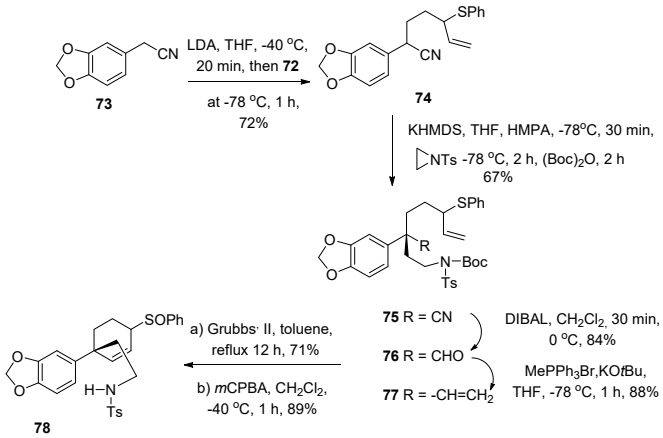
ii) Synthesis of crinane utilizing an allylic sulfoxide for the construction of a hydroindole ring, by Raghavan and Ravi: In their new approach to the crinane alkaloids, Raghavan and Ravi made use of a vinylogous Pummerer reaction to form the octahydroindole central core [21]. Their synthesis commenced by treating the monoprotected 1,3-propanediol **69** with diphenyl disulfide under conditions developed by Hata [22] to afford sulfide



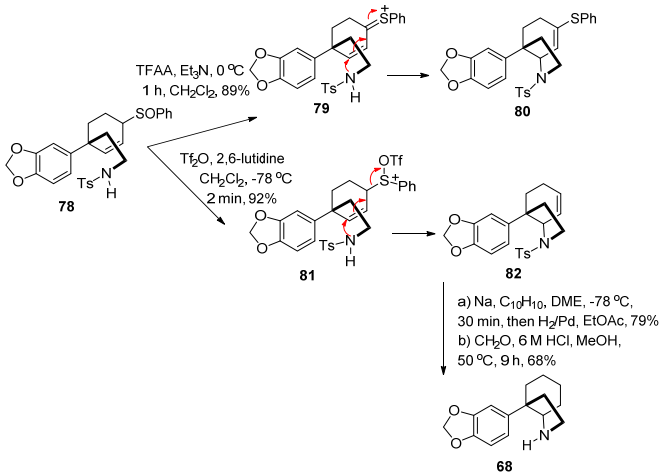
Scheme 10: Synthesis of vinyl iodide **72**.

70. Chlorination α- to the sulfur atom was achieved using *N*-chlorosuccinamide and the product was treated with vinyl magnesium bromide to afford the allylsulfide **71** in 95% yield. Acid catalysed deprotection of the silyl ether, followed by iodination of the alcohol produced the vinyl iodide **72** in 70% yield for the two steps (Scheme 10).

The commercially available benzylic cyanide **73** was then monoalkylated with iodide **72** under basic conditions to afford sulfide **74** in 72% yield. The crucial quaternary carbon was then generated by treatment of **74** with the powerful base KHMDS in THF containing HMPA and tosyl aziridine, followed by Boc protection to give the rather congested cyanosulfide **75** in 67% yield. Transformation of the cyano group of **75** into the aldehyde **76** was efficiently effected with DIBAL-H in dichloromethane in 84% yield, which was followed by an equally efficient one-carbon homologation under Wittig conditions to form the diene **77** (88%). This compound was perfectly set up for a RCM using Grubbs' II catalyst to afford the corresponding sulfide with simultaneous loss of the Boc group in 71% yield and was followed by the oxidation of the latter sulfide with *m*CPBA to generate the epimeric sulfoxides **78** in 89% yield (Scheme 11).



Scheme 11: Synthesis of sulfoxide **78**.

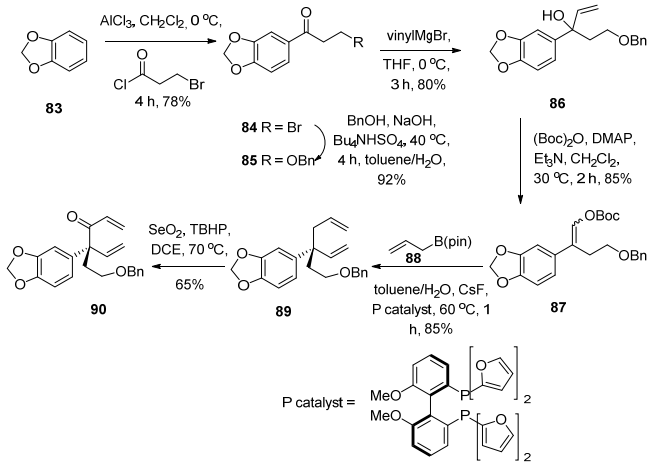


Scheme 12: Synthesis of crinane **68** and other intermediates.

At this point of the protocol, the sequence was developed in two different ways. Firstly, treatment of **78** with TFAA in Et_3N produced an intermediate sulfonium salt which then converted into the sulfenium ion **79** to undergo the Pummerer-type ring closure reaction and produce cyclohexene **80**, a most valuable intermediate

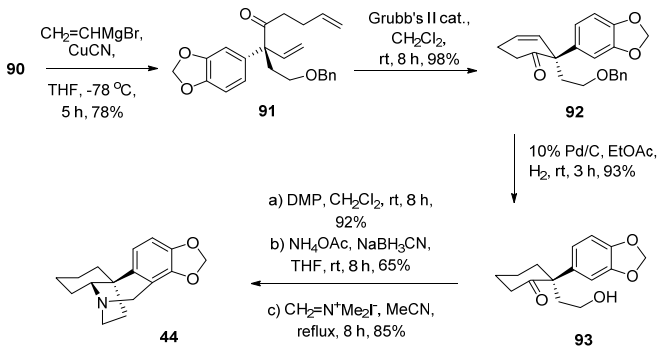
for the synthesis of numerous members in the crinine family. Secondly, sulfoxide **78**, when treated with triflic anhydride in 2,6-lutidine and DCM at –78 °C afforded the sulfonium salt **81**, followed by stereochemically controlled intramolecular cyclisation with loss of sulfenyl triflate to afford the mesembrane skeleton **82** in 92% yield. Next, removal of the Ts group was effected with sodium naphthalimide, reduction of the double bond by H_2/Pd and final treatment with acidified formalin resulted in an excellent yield of the natural product crinane **68** (Scheme 12).

iii) Asymmetric syntheses of (-)-crinane and (+)-4a-dehydroxycrinamabine, by Wang and co-workers: Wang and co-workers employed a new approach for installation of the crucial chiral quaternary centre for the crinane-type alkaloids they described as a palladium-catalysed asymmetric allyl-allyl cross coupling reaction [23]. Their synthesis began by Friedel-Crafts acylation between commercially available 1,3-benzodioxole **83** and 3-bromopronanoic acid chloride to produce ketone **84** (78%). This was followed by transformation of the latter into the corresponding benzyloxy analogue **85** (92%). A Grignard reaction with vinyl magnesium bromide afforded alcohol **86** (80%), which when treated with $(Boc)_2O$ in Et_3N afforded the rearranged olefin **87** (85%) in an *E/Z* ration of 4:1. The vital allyl-allyl cross coupling between **87** and allyl B(pin) **88** was then optimized with an interesting phosphorous catalyst to give the pivotal diene **89** (85%) (ee 94%). Selenium(IV) dioxide oxidation of the latter with an excess of *t*-butyl hydroperoxide (TBHP) gave the α,β-unsaturated ketone **90** (65%) (Scheme 13).



Scheme 13: Synthesis of dienone **90**.

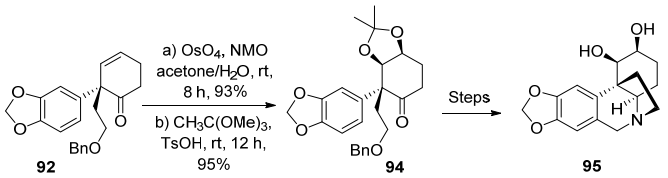
Michael addition of vinyl magnesium bromide to ketone **90** in the presence of CuCN at -78 °C provided the keto olefin **91** (78%). Next RCM using Grubbs' II catalyst afforded the six-membered



Scheme 14: Synthesis of (-)-crinane **44**.

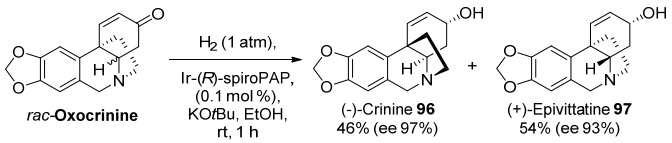
ring intermediate **92** (98%). Catalytic hydrogenation then removed the benzyl group and reduced the double bond to afford the keto alcohol **93** and its hemiacetal (93%). Dess-Martin periodinane oxidation of the primary alcohol **93** produced the corresponding aldehyde (92%), followed by a reductive amination with ammonium acetate and sodium cyanoborohydride. Finally, a Pictet-Spengler protocol with dimethylmethylene ammonium iodide (Eschenmoser's salt) produced (-)-crinane **44** (55% for the 2 steps) (Scheme 14).

The authors next developed a method, using intermediate **92**, for the synthesis of the more complex crinamabine. Thus **92** was dihydroxylated with OsO_4 and NMO to afford a single diastereomer which was protected as the acetonide **94** (88% for the 2 steps). Through an analogous set of reactions used for conversion of **93** into **44** illustrated in Scheme 14, ketone **94** was converted into (+)-4a-dehydroxycrinamabine **95** in 20% yield (for 5 steps), the final one being treatment with concentrated hydrochloric acid in methanol (Scheme 15).



Scheme 15: Synthesis of (+)-4a-dehydroxycrinamabine **95**.

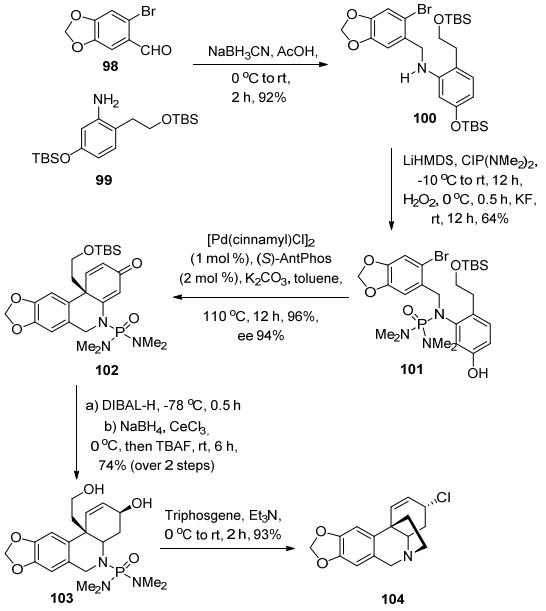
iv) Bioinspired enantioselective synthesis of crinine-type alkaloids via iridium-catalyzed asymmetric hydrogenation of enones, by Zhou and co-workers: Zhou and co-workers developed an interesting iridium catalyst viz., Ir-SpiroPAP and applied it for the bioinspired asymmetric hydrogenation of racemic oxocrinine to produce the *cis* and *trans* products **96** and **97** (Scheme 16) [24]. These compounds were then converted into their benzoyl esters in order to simplify their chromatographic separation after which hydrolysis of the pure isolates afforded (-)-crinine **96** and (+)-epivittatine **97**. This process was instrumental in the group preparing an extensive library of crinine-type alkaloids on a gram scale.



Scheme 16: Asymmetric hydrogenation to form crinine **96** and epivittatine **97**.

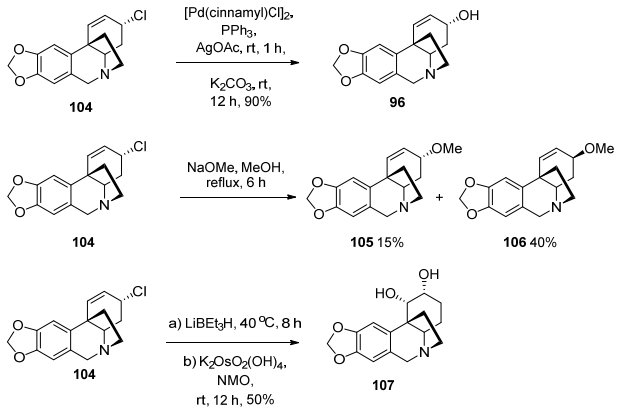
v) Syntheses of (-)-crinine and (-)-aspidospermidine, and the formal synthesis of (-)-minfiensine using enantioselective intramolecular dearomative cyclizations, by Tang and co-workers: Tang and co-workers developed a most useful asymmetric dearomative cyclisation protocol to generate the core nucleus of the crinine type Amaryllidaceae alkaloids by employing a mixture of palladium and phosphorus catalysts [25]. Their synthetic route started by reductive amination of the product formed by reaction between 6-bromopiperonal **98** and aniline **99** to afford amine **100** (93%) after reduction of the initial imine. This was followed by conversion of the nitrogen into the phosphoramide group with LiHMDS/CIP$(NMe_2)_2$/H_2O_2. Subsequent treatment with KF/tetraethylene glycol selectively removed the aryl TBS group to afford the *N*-protected phenol **101** (64%). The pivotal intramolecular dearomative cyclisation of the bromophenol **101**

catalysed by palladium and (*S*)-AntPhos produced the tetracycle **102** with the desired quaternary carbon in 96% yield and with an ee of 94%. Selective enamide double bond reduction of **102** with DIBAL-H at -78 °C was followed by Luche reduction of the ketone and removal of the primary TBS protecting group with TBAF produced the allylic alcohol **103** (74% for 2 steps). A rather clever protocol involved treatment of allylic alcohol **103** with triphosgene/Et_3N which removed both the *N*-protecting group and activated the primary alcohol as the alkyl chloride which then underwent the intramolecular cyclisation with the nucleophilic nitrogen atom to form the crinine motif **104** (93%). One needs to be aware of the inversion of stereochemistry of the secondary alcohol when converted into the chloride. This intermediate now served as a general intermediate for a number of further transformations into other crinine alkaloids (Scheme 17).



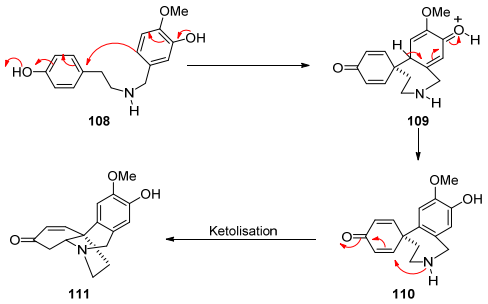
Scheme 17: Synthesis of chloride **104**

Thus, after some trial and error, treatment of chloride **104** with the same palladium catalyst as earlier, PPh_3 and AgOAc afforded the stereoselective allylic acetate which was hydrolysed to (-)-crinine **96** (90%). On the other hand, methanolysis of allylic chloride **104** afforded buphanisine **105** (15%) and epibuphanisine **106** (40%), while reducing it with $LiEt_3BH$ at 40 °C for 8 h, followed by a *cis*-dihydroxylation protocol gave amabiline **107** (50% for 2 steps) (Scheme 18).



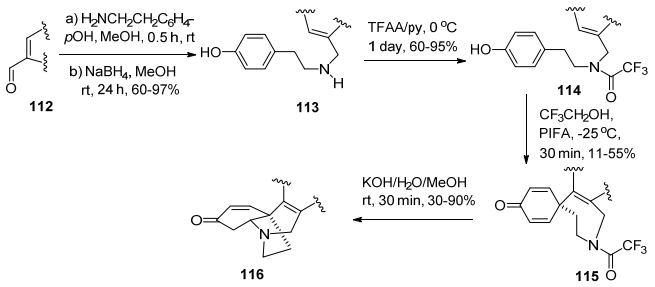
Scheme 18: Synthesis of (-)-crinine **96** and some of its analogues from a common precursor **104**

vi) 5,10*b*-Ethanophenanthridine alkaloid-inspired novel bicyclic ring systems, by Frolova, Kornienko and co-workers: Frolova, Kornienko and co-workers made good use of a biomimetic approach for the synthesis of the crinine skeleton [26]. This approach is based on the intramolecular *para-para* oxidative coupling of *O*-methylnorbelladine **108**, followed by a subsequent intramolecular Michael cyclisation of the spiro bicyclic intermediate **109** to afford the noroxomaritidine skeleton **111** after aromatization of the intermediate **110** (Scheme 19).



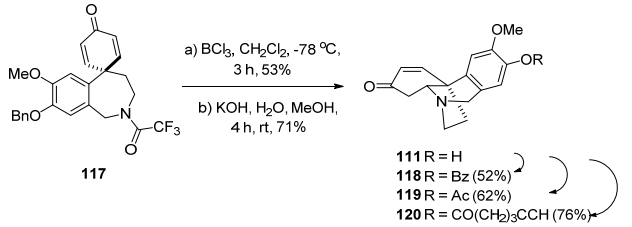
Scheme 19: Proposed biosynthesis of the crinine skeleton.

Over the years, many laboratory methods have been developed to mimic the oxidative coupling *vide infra* which has proved to be one of the most efficient protocols for synthesizing crinine 5,10b-ethanophenanthridine ring systems. In their approach, Henry *et al.* reacted appropriate aldehydes **112** (partial structures of generic alkaloid aromatic systems illustrated) with tyramines to produce the corresponding imines which without isolation were efficiently reduced to the amines **113** in yields of between 60-97%. It was found that converting the latter amines into their trifluoroacetamides **114** in 60-95% yields served best, both to protect the molecule and to serve an important purpose later. Phenyliodine(III)bis(trifluoroactate) (PTFA) in 2,2,2-trifluoro-ethanol facilitated the regioselective oxidative *para-para* coupling providing the corresponding spirocyclic dienones **115** in yields ranging from 11-55%. Treatment of these dienones with KOH in aqueous methanol removed the protecting group under very mild conditions and released the nucleophilic amine nitrogen for the intramolecular Michael condensation on the α,β-enone system to afford the various 5,10b-ethanophenanthridine analogues **116** in yields of 30-90% (scheme 20).



Scheme 20: General protocol for the formation of crinine-type alkaloids. The squiggly lines represent the general aromatic systems of the alkaloids.

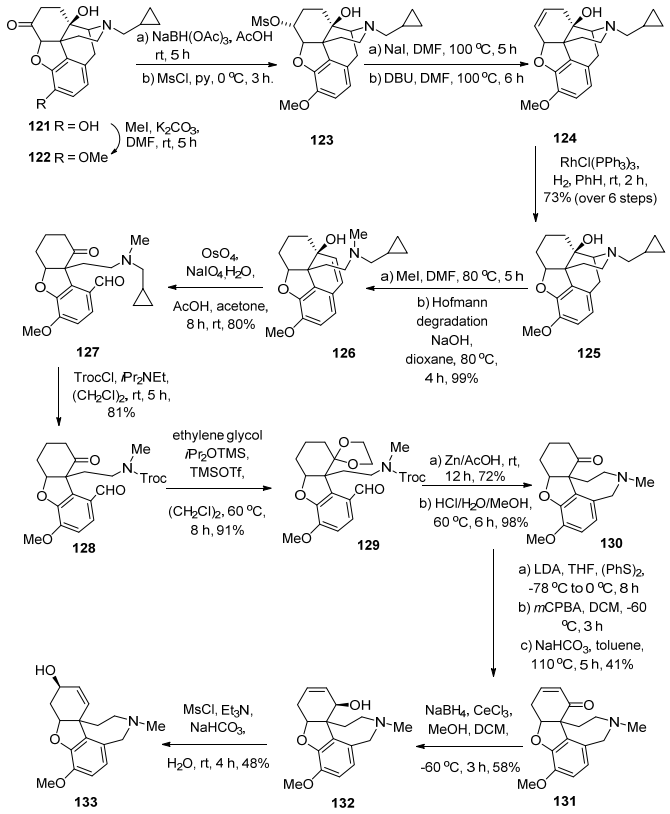
In order to obtain further analogues of 5,10b-ethanophenanthridenes for biological evaluation, the group debenzylated intermediate **117** by treatment with BCl_3 at -78 °C in CH_2Cl_2, followed by the intramolecular Michael cyclisation in methanolic potassium hydroxide to afford noroxomaritidine **111**, which in turn was converted under standard conditions into the benzoyl analogue **118**, acetyl analogue **119** and ester **120**. It was also possible to convert the carbonyl group of **111** into the oxime (not illustrated) under standard conditions in 70% yield (Scheme 21).



Scheme 21: Synthesis of noroxomaritidine **111** and its conversion into analogues **118**, **119** and **120** under standard conditions.

c) Galanthamine-scaffold alkaloids

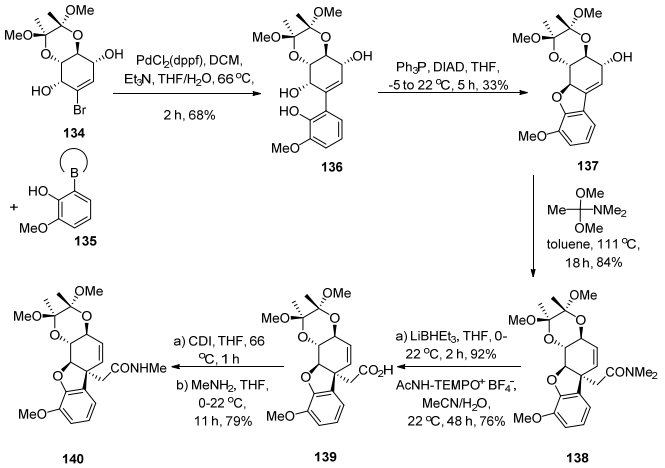
i) The application of a specific morphinan template to the synthesis of (-)-galanthamine, by Yamamoto and co-workers: In an initially rather laborious and lengthy route to the Amaryllidaceae alkaloid, (-)-galanthamine (**133**), (For a recent review on this particular alkaloid, see the book chapter by Hudlicky and co-workers [28]), the group of Yamamoto and co-workers started with the commercially available naltrexone **121** which was easily methylated with MeI to afford the corresponding methyl ether **122** [27]. In the Yamamoto work, the ketone group was reduced with sodium triacetoxyborohydride and the resulting α-hydroxy product was



Scheme 22: Synthesis of galanthamine **133**.

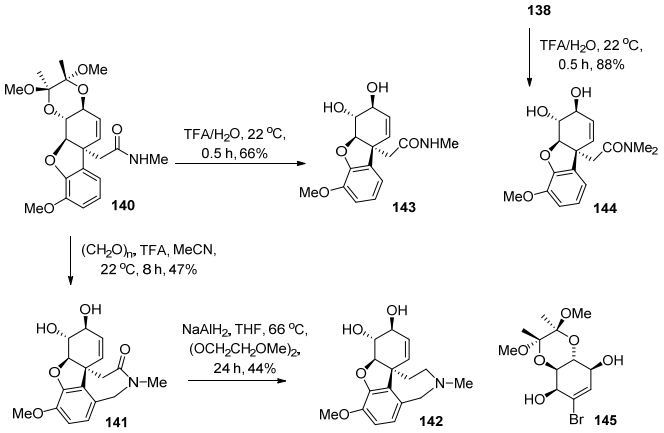
mesylated with mesyl chloride in pyridine to afford the mesyl ether **123**. This was followed by sodium iodide treatment at 100°C in DMF and then in DBU at 100°C as well, to afford an isomeric mixture of the two possible cyclohexene products **124**. Finally, reduction of this mixture using Wilkinson's catalyst in benzene afforded the single pentacylic molecule **125** (73% for the six steps). Hofmann elimination protocols applied to compound **125** lead to the all-important 9-17 bond cleavage to give the cyclohexene **126** (99%). Lemieux-Johnson oxidation of **126** resulted in removal of the C-9 to afford keto-aldehyde **127** (80%) which upon treatment with TrocCl in diisopropyl ethyl amine resulted in formation of the *N*-Troc analogue **128** (81%). This keto-benzaldehyde was chemoselectively protected at the ketone as the acetal **129** (90%). Removal of the Troc protecting group on the nitrogen atom was achieved with the use of Zn-acetic acid after which it subsequently underwent ring closure with the aromatic aldehyde group to form the new 7-membered ring of **130** (98%). Introduction of the double bond in the cyclohexanone ring was effected by treatment with LDA and diphenyl disulfide addition with subsequent oxidation with *m*CPBA at -78 °C to afford the sulfoxide. This underwent the anticipated β-elimination to afford the desired α,β-unsaturated cyclohexenone **131** (41% for the 3 steps). Luche reduction of enone **131** gave a separable mixture of the anticipated diastereomers with **132** being the major (48%). Finally mesylation of **132** with MsCl in pyridine, followed by treatment with aqueous sodium hydrogen carbonate afforded a diastereomeric mixture of (-)-galanthamine **133** (major 48% and minor 23%) (Scheme 22).

ii) The synthesis of derivatives and analogues of (-)- and (+)-galanthamine, by Banwell and co-workers: Banwell and co-workers developed an effective and neat protocol for the synthesis of analogues of (-)- and (+)-galanthamine **133** in order to evaluate their acetylcholine esterase inhibition potential [29]. The group's synthesis commenced by the coupling between vinyl bromide **134** and boronic ester **135** with $PdCl_2$ catalyst to afford the arylated cyclohexene **136** (68%). An intramolecular Mitsunobu reaction afforded the acid-sensitive isobenzofuran **137** (33%). Subjecting the latter benzofuran to Eschenmoser-Claisen conditions afforded amide **138** (84%). Reduction of the amide **138** with $LiEt_3BH$ in THF produced the primary alcohol (92%) which was oxidized to the corresponding carboxylic acid **139** using the Bobbit and Bailey protocol. Conversion of acid **139** into the corresponding *N*-methyl amide **140** (79%) was accomplished by CDI activation of the acid followed by treatment with methylamine (Scheme 23).



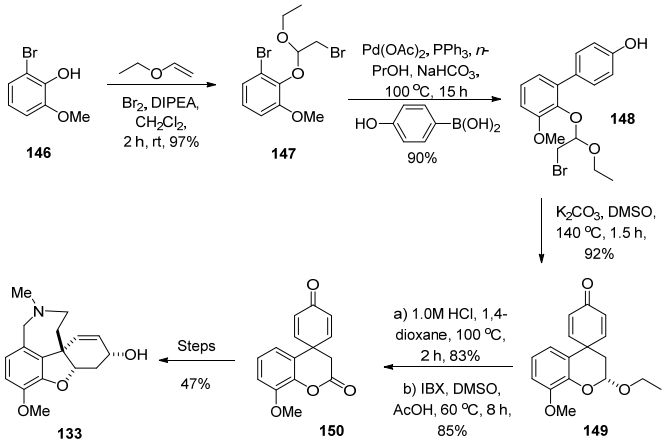
Scheme 23: Synthesis of amide **140**.

Exposure of amide **140** to a modified Pictet-Spengler protocol with paraformaldelyde afforded the seven-membered lactam **141** (47%) with concomitant loss of the Ley acetal moiety. Reduction of the lactam carbonyl group was effected with sodium bis (2-methoxy ethoxy) aluminium dihydride to form the azepine **142** (44%). On the other hand, hydrolysis of intermediate **140** with aqueous TFA gave diol analogue **143** (66%) while similar hydrolysis of intermediate **138** afforded the dimethylamino amide **144** (88%). By making use of the enantiomeric isomer **145**, the enantiomeric analogues were synthesized using the same protocol illustrated in Scheme 24.



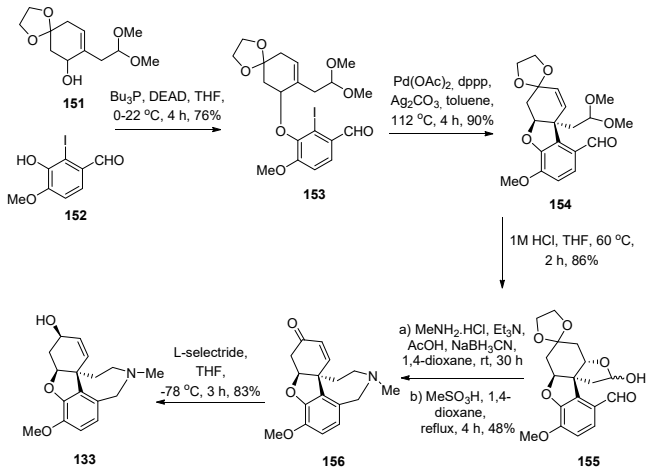
Scheme 24: Formation of analogues of galanthamine.

iii) Synthesis of Guillou's galanthamine intermediate, by Zeng and co-workers: Zeng and co-workers developed a new synthesis for Guillou's galanthamine intermediate **150** which requires four further known steps for the final formation of *rac*-galanthamine **133** [30]. This was in response to the inherent shortcomings in the original synthesis of Guillou *et al*. [31] Thus phenol **146** was treated with ethyl vinyl ether and Br_2 in DCM in the presence of DIPEA to afford ether **147** (97%) which subsequently underwent a Suzuki cross coupling reaction with *p*-hydroxybenzeneboronic acid catalysed by $Pd(OAc)_2/PPh_3$ in *n*-PrOH/H_2O/$NaHCO_3$ to give the biphenyl molecule **148** (90%). Deprotonation of the phenol moiety with K_2CO_3 in DMSO at 140 °C then set up conditions for the *para*-alkylation via an intramolecular cyclisation to form the quaternary spiro tricyclic intermediate **149** (92%). Removal of the ethoxy group from the acetal moiety was achieved by treatment with 1.0 M HCl/1,4-dioxane at 100 °C for 2 h (83%) and subsequent oxidation of the hemiacetal with 2-iodoxybenzoic acid (IBX) in AcOH smoothly converted it into the spiro-lactone **150** (85%). Four remaining known steps applied to Guillou's intermediate **150** provided *rac*-galanthamine **133** in 47% yield for the 4 steps (Scheme 25).



Scheme 25: Synthesis of Guillou's galanthamine intermediate **150**.

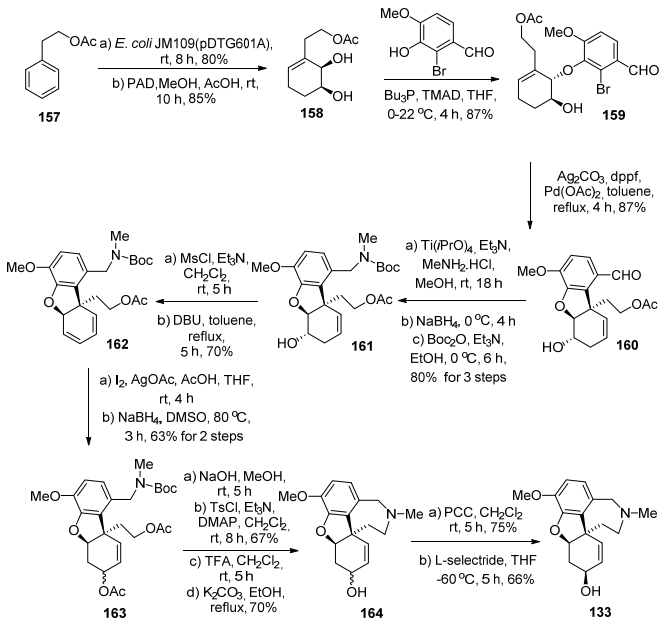
iv) Synthesis of galanthamine, by Banwell and Nugent: Banwell and Nugent, using commercially available cyclohexane-1,4-dione monoethylketal to prepare **151**, developed a short efficient synthesis of *rac*-galanthamine **133** [32]. To this end, intermolecular Mitsunobu condensation between ketal **151** and the iodated dervative of isovanilin **152** produced the expected ether **153** (76%). This was followed by an intramolecular Heck reaction with $Pd(OAc)_2$, dppp and Ag_2CO_3 in toluene at 110 °C for 4 h to afford the quaternary carbon-centered benzofuran **154** (90%). After some investigations, it was found that the most efficient way forward involved treatment of the doubly protected aldehyde **154** with 1 M HCl in THF at 60 °C for 2 h which hydrolysed both the acetal and ketal functionalities to afford the ketoaldehyde **155** (86%) which is the key intermediate in the synthesis of (±)-narwedine **156**. In an improved protocol, it was discovered that treatment of aldehyde **155** with methylamine hydrochloride in the presence of $NaBH_3CN$ in Et_3N and AcOH resulted in formation of a boron complex of narwedine, which was subsequently cleaved with methanesulfonic acid in refluxing 1,4-dioxane to afford the *rac*-narwedine **156** (48% for the 2 steps). Finally, reduction of the ketone function of narwedine **156** with L-selectride afforded *rac*-galanthamine **133** (83%) (Scheme 26).



Scheme 26: Synthesis of *rac*-galanthamine **133**.

v) Chemoenzymatic total synthesis of (+)-galanthamine and (+)-narwedine, by Endoma-Arias and Hudlicky: Endoma-Arias and Hudlicky made efficient use of an initial microbial dihydroxylation protocol in their synthesis of (-)-galanthamine **133** starting from phenylethylacetate **157** [33]. *E.coli* and potassium azodicarboxylate (PAD) were employed for the efficient microbial dihydroxylation of **157** in MeOH/AcOH to afford cyclohexanediol **158** (68%) which was followed by an intermolecular Mitsunobu reaction with 2-bromoisovanilin using Bu_3P and TMAD as reagents in THF to afford ether **159** (87%) as a result of the more reactive allylic alcohol functionality. Then followed an intramolecular Heck reaction of **159** with $Pd(OAc)_2$, Ag_2CO_3 and dppf under reflux in toluene to produce the tricyclic scaffold **160** (87%). Reductive amination of the free aldehyde group was effected by treatment with methylamine hydrochloride and $NaBH_4$ after which the amine was protected as the Boc analogue **161** (80% for the three steps). In order to install the C-6-OH, an elimination/hydrogenation protocol was developed. Thus mesylation of alcohol **161** with MsCl in Et_3N, followed by an elimination protocol with DBU under reflux in toluene produced diene **162** (70%). A Prevost reaction of diene **162** gave a diastereomeric mixture of iodo acetates which were immediately reduced with $NaBH_4$ in DMSO at 80 °C to give a 2:1 mixture of diastereomeric acetates **163**. Hydrolysis of the acetate groups with aqueous NaOH in MeOH was followed by reprotection of the primary alcohol as the OTs analogue (67%) with TsCl. Removal of the Boc group from the nitrogen with TFA in DCM and evaporation of the solvents was followed by treatment of the residue with K_2CO_3 in EtOH and then heating under reflux lead to formation of epimeric *ent*-galanthamines **164** (70%) in a 2:1 ratio and favouring the 6-β epimer. Oxidation of the epimeric mixture

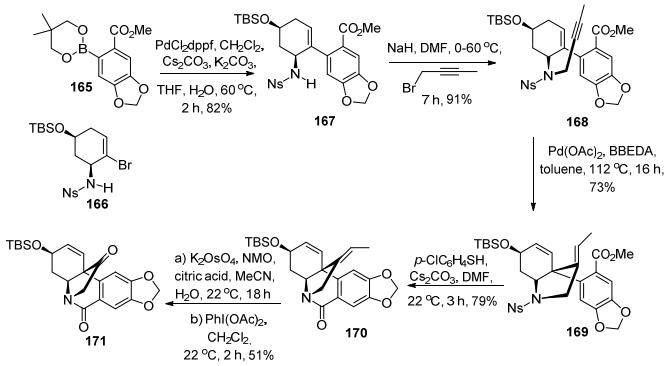
164 with PCC in DCM at rt for 5 h afforded the corresponding *ent*-narwedine (75%) (not illustrated) and finally stereoselective reduction with L-selectride in THF at -60 °C for 5 h gave (-)-galanthamine **133** (66%) (Scheme 27).



Scheme 27: Synthesis of (-)--galanthamine **133**.

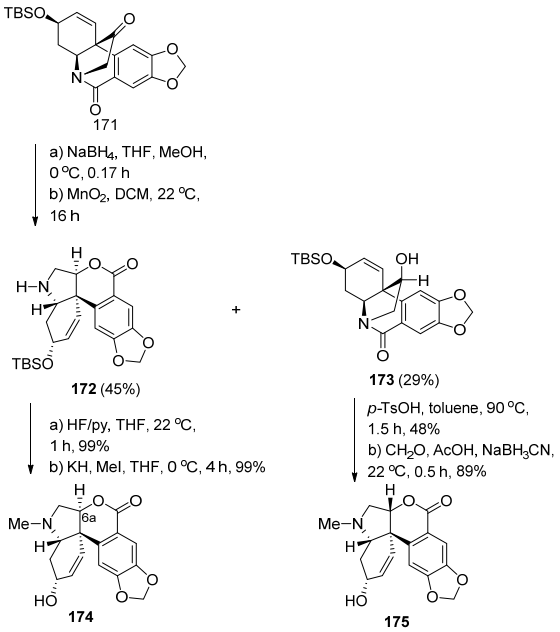
d) Tazettine-scaffold alkaloids

i) Total synthesis of (±)-3-O-demethylmacronine through rearrangement of a haemanthidine alkaloid framework precursor, by Banwell and co-workers: Banwell and co-workers established an elegant 10-step synthesis of racemic 3-*O*-demethymacronine, a tazettine type alkaloid, which embodied the incorporation of a strained lactam scaffold [34]. Suzuki-Miyaura cross-coupling of the known boronate ester **165** with the known cycloalkenyl bromide **166** afforded the desired cyclohexene **167** (83%), which was readily propargylated at the nitrogen atom with 1-bromo-2-butyne in the presence of NaH in DMF to give **168** (91%). An intramolecular Alder-ene (IMAE) cyclization catalysed by $Pd(OAc)_2$ and supported by the powerful σ-donating ligand *N*,*N*′-*bis*(benzylidene)ethylenediamine (BBEDA) under reflux in toluene produced the hexahydroindole **169** (73%). In a most interesting intramolecular cyclisation, the Fukuyama protocol for the removal of the nosylate protection group also encouraged lactamization with the pendant ester to afford the strained lactam **170** (79%). Chemoselective dihydroxylation of the exocyclic double bond under Bäckvall conditions, followed by oxidation with iodosobenzene diacetate gave the equally strained ketoamide **171** (51%) for the two steps) (Scheme 28).



Scheme 28: Synthesis of ketamide **171**.

Reduction of lactam **171** with $NaBH_4$ in methanol produced a mixture of compounds, which after MnO_2 oxidation afforded a separable mixture of lactone **172** as the major product (45%), and lactam **173** as the minor product (29%). Treatment of lactone **172** with HF-pyridine in THF removed the TBS group (99%) and *N*-methylation was chemoselectively performed using KH and MeI in THF to afford the C-6a epimer of (±)-3-*O*-demethylmacronine **174** (99%). On the other hand, the haemanthidine-based hydroxylactam **173** was treated with TsOH to induce a pivotal rearrangement not yet fully understood to produce the naturally occurring *rac*-C-6a stereoisomer of macronine (not illustrated) (48%) and *N*-methylation in this case had to be effected by a reductive methylation protocol using formaldehyde and sodium cyanoborohydride to ultimately produce (±)-3-*O*-demethylmacronine **175** (89%) (Scheme 29).

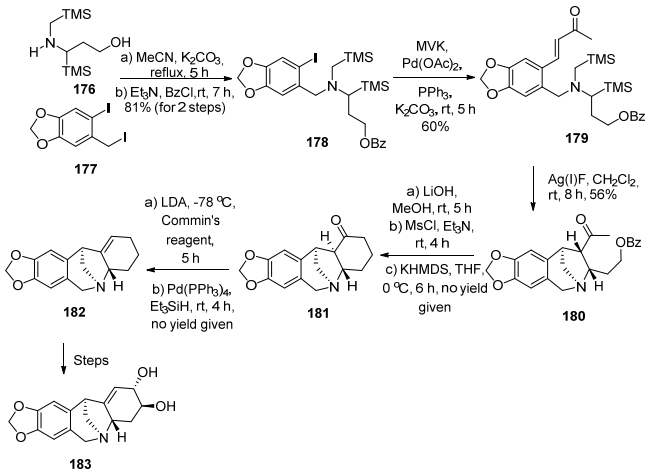


Scheme 29: Synthesis of the C-6a-epimer of *rac*-3-O-demethylmacronine **174** and *rac*-3-O-demethylmacronine **175**.

e) Montanine-scaffold alkaloids

i) Synthesis of *rac*-pancracine by [3+2] cycloaddition of non-stabilized azomethine ylides, by Pandey *et al.*: In this paper by Pandey *et al*. they describe, without providing full details, their use of a [3+2] cycloaddition of a non-stabilized azomethine ylide (AMY) in a strategy for the synthesis of *rac*-pancracine which is provided here as an example [35]. The bis TMS amino alcohol **176** was *N*-alkylated with benzyl iodide **177** in refluxing MeCN in the presence of K_2CO_3, followed by benzoylation of the primary alcohol to afford **178** (81%). A Heck coupling of **178** with 8 equivalents of MVK gave enone **179** (60%), which when converted into the azomethine ylide with Ag(I)F in DCM underwent the [3+2] cycloaddition, to smoothly produce the tetracyclic molecule **180** (56%). Upon debenzylation with LiOH/MeOH, **180** was converted into its C12 epimeric alcohol (not shown). Conversion of the primary alcohol into the mesylate with $MsCl/Et_3N$ was followed by intramolecular cyclisation under kinetic control using KHMDS to produce the pentacyclic **181** during which stage epimerization had occurred. This compound was converted into the enol triflate by

treatment with LDA and Commin's reagent after which final reduction of the latter with $Pd(PPh_3)_4$ and EtSiH produced the corresponding cyclohexene **182**. Finally, following the known procedure, this latter compound was transformed into *rac*-pancracine **183** to represent a new formal synthesis for this alkaloid (Scheme 30). For another montanine-related synthesis see Scheme 48.



Scheme 30: Synthesis of *rac*-pancracine **183**.

f) Phenanthridone-scaffold alkaloids

i) Synthesis of (+)-*trans*-dihydrolycoricidine by an organocatalytic enantioselective Friedel-Crafts reaction, by Kato and co-workers: Prior to the synthesis by Kato and co-workers of the highly anti tumour Amaryllidaceae alkaloid viz., (+)-*trans*-dihydrolycoridine (**184**) [36], there were five other groups who had achieved this milestone using a host of different innovative protocols (Figure 3).

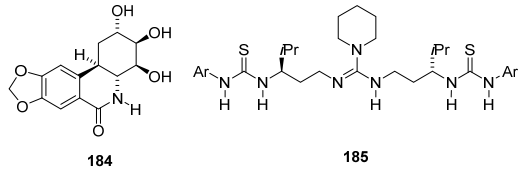
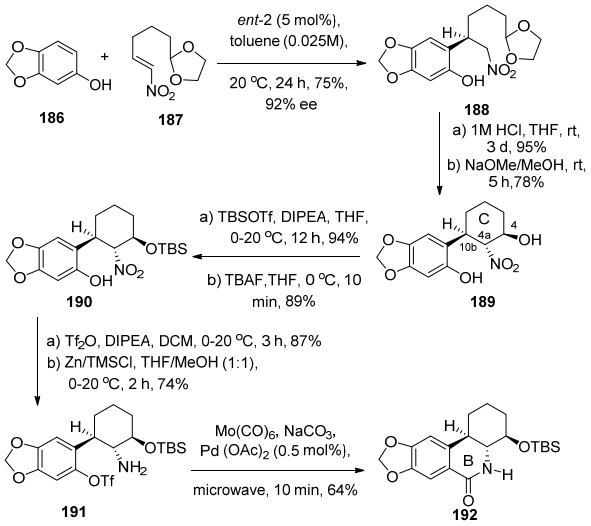
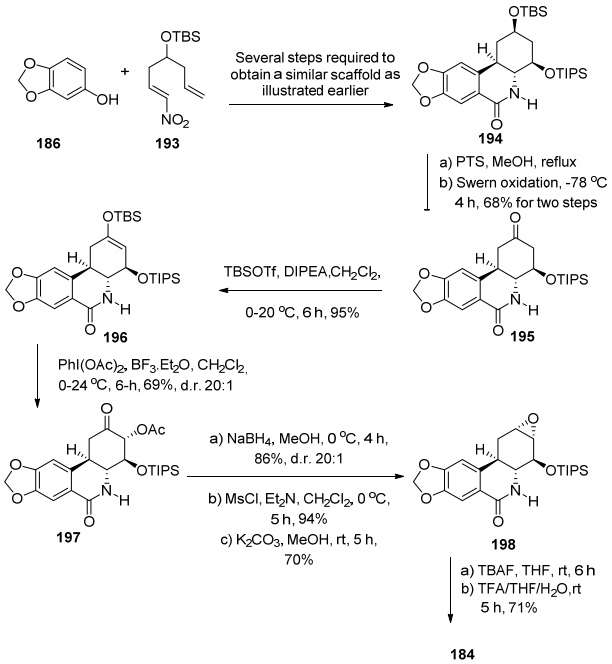


Figure 3: (+)-*trans*-Dihydrolycoridine **184** and catalyst **185**.

Their synthesis commenced with the all-important enantioselective 1,4-Friedel-Crafts (FC) condensation developed by the group between enol **186** and an appropriately protected nitro-olefin **187** in the presence of 5 mol % of the organocatalyst **185** in toluene at 20 °C to produce a 75% yield of the 1,4-FC adduct **188** with a most acceptable 92% ee. To release the aldehyde, **188** was treated with 1M HCl followed by an intramolecular Henry reaction between the nitromethyl carbon and the aldehyde in methanolic sodium hydroxide to afford the nitro alcohol **189** (74% for the 2 steps) as a single diastereomer. The bonds of the three contiguous centres *viz* C4, C4a and C10b in ring C were all in the thermodynamically more stable equatorial positions. Both hydroxyl groups were protected as their TBS ethers followed by chemoselective deprotection of the phenolic TBS ether with TBAF to yield phenol **190** (84% for the two steps). Conversion of the phenolic group into its triflate was followed by reduction of the nitro group with Zn and TMSCl to afford the differentially protected amine **191** (64% for the 2 steps). The group found that the best way to facilitate the palladium-catalysed CO insertion for the construction of ring B was to use $Mo(CO)_6$ as the CO source under microwave heating which afforded the corridine skeleton **192** (64%) (Scheme 31). These researchers were however, unable to introduce an oxygen functionality at C2 and C3 of this latter intermediate **192** and thus decided to start from a different nitro-olefin.



Scheme 31: Construction of rings B and C of the corridine nucleus.

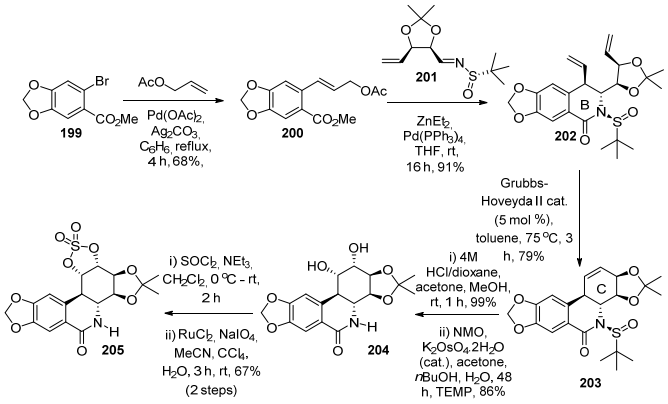


Scheme 32: Synthesis of (+)-*trans*-dihydrolycoricidine **184**.

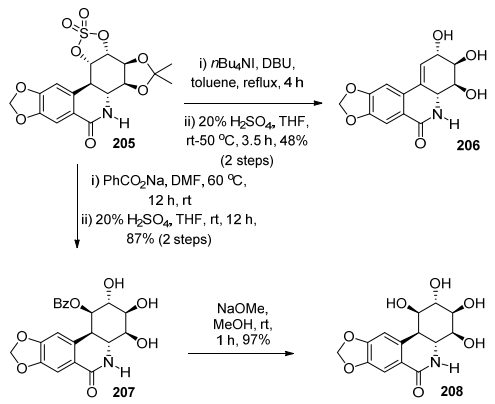
To this end, a similar 1,4-FC condensation between **186** and the oxygenated racemic nitro-olefin **193** was undertaken and following the proven analogous protocol employed before, the corresponding coricidine intermediate **194** was obtained. The TBS ether of **194** was selectively deprotected by treatment with catalytic PTS in methanol followed by Swern oxidation to yield the corresponding ketone **195** (68% for the two steps). In order to activate C3 for hydroxylation, ketone **195** was treated with TBSOTf in diisopropylethylamine at 0 °C to form the regioselective enol ether **196** (95%). Next followed a highly stereoselective instalment of an acetoxy group at C3 on treatment with phenyliodonium diacetate for a good yield of acetate **197** (69%). $NaBH_4$ reduction of ketone **197** gave the corresponding C2 β-alcohol as a consequence of axial attack of the hydride. Mesylation of the C2 β-hydroxyl group with methane sulfonyl chloride followed by base-catalysed ring closure

afforded epoxide **198** (62% for the 2 steps). Finally, the TIPS protecting group was removed with TBAF and the resulting epoxide was both regio- and stereoselectively hydrolysed with TFA to provide (+)-**184** (71% for the 2 steps) (Scheme 32).

ii) Asymmetric cinnamylation of *N-tert*-butanesulfinyl imines with cinnamyl acetates for the total syntheses of (+)-lycoricidine and (+)-7-deoxypancratistatin, by Sun and co-workers: In work related to that described earlier in this review, Sun and co-workers recently described a highly diastereoselective palladium catalysed cinnamylation of *N-t*-butanesulfinyl imines for the synthesis of two related Amaryllidaceae isocarbostyrils [14]. Thus commencing from bromide **199**, the Ag_2CO_3 promoted Heck reaction afforded the cinnamyl acetate **200** (68%). This was followed by treatment with a previously prepared (*S*)-*N-tert*-butanesulfinyl imine **201** from iodoribose, which underwent a cinnamylation followed by a cyclisation sequence the group pioneered to afford the *trans*-fused lactam **202** as a single diastereomer in an impressive 91% yield, thereby accomplishing the construction of the B ring of the target alkaloids. Ring C was then formed through a RCM reaction employing the Grubbs-Hoveyda II generation catalyst to actually precipitate the product **203** from the toluene solution in 79% yield. Removal of the *t*-butanesulfinyl group was achieved (99%) with 4 M HCl in dioxane during which it was necessary to add acetone to suppress the loss of the acetonide protecting group. This was followed by the *cis*-dihydroxylation of the C1-C2 double bond with potassium osmium tetroxide to afford the exo-diol **204** in an 86% yield with a diastereoselectivity of 13:1. The pivotal intermediate **205** was then generated by treatment of diol **204** with firstly $SOCl_2$ and then oxidation of the intermediate with $RuCl_3/NaIO_4$ to give the desired cyclic sulfate **205** (67%) (Scheme 33).



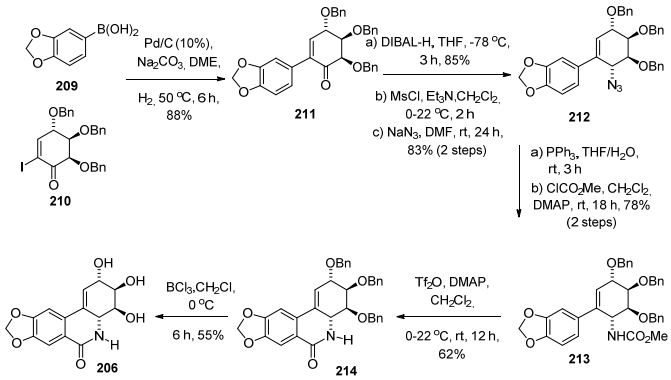
Scheme 33: Synthesis of rings B and C for lycorine-type alkaloids/isocarbostyrils.



Scheme 34: Synthesis of (+)-lycoricidine **206** and (+)-7-deoxypancratistatin **208**.

From the pivotal intermediate **205**, two pathways were developed for further transformations as follows: a) ring opening of the sulfate moiety using *n*-Bu_4NI at the less hindered C1 position afforded the *trans* iodo intermediate which underwent an *anti*-elimination and acid hydrolysis to afford (+)-lycoricidine **206** (48%); b) a similar *trans*-diaxial ring opening of the cyclic sulfate **205** was effected with sodium benzoate at the C1 position, followed by mild acid hydrolysis to afford benzoate **207** (87%). Hydrolysis of this ester viz., **207** with sodium methoxide in MeOH gave the (+)-7-deoxypancratistatin **208** (57%) (Scheme 34).

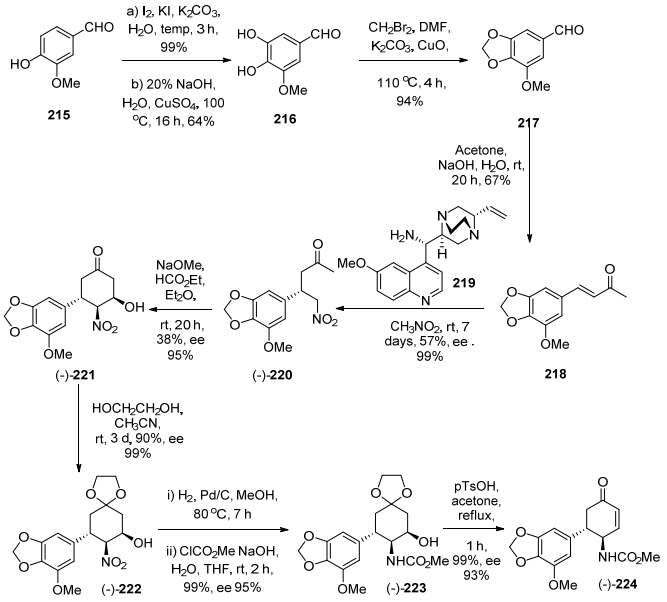
iii) A chiron-based approach to the total synthesis of (+)-lycoricidine, by Shaw and Saidhareddy: Shaw and Saidhareddy developed an efficient synthesis for (+)-lycoricidine **206**, a member of the pancratistatin amaryllidaceae isocarbostyril family [37]. Their synthesis began with a Suzuki-Miyaura cross-coupling between boronic acid **209** and the α-iodoenone **210**, the latter being derived from methyl α-D-galactopyranoside, in the presence of Pd/C and Na_2CO_3 in DME to produce the new enone **211** (88%). DIBAL-H reduction of the ketone moiety at -78 °C generated the corresponding alcohol (85%) in which the 6-OH was *syn* to the adjacent 5-OBn of the cyclohexene ring. Mitsunobu reaction of the latter was effected by conversion into the corresponding mesylate with MsCl and then subjecting it to an azidation with NaN_3 in DMF to afford the inverted azide **212** (83%). Reduction of the azide moiety to the amine was achieved by treatment with PPh_3, followed by activation with methyl chloroformate and DMAP to provide **213** (78%). A modified Bischler-Napieralski cyclisation with Tf_2O and DMAP in DCM at 0 °C then produced the tetracycle **214** (62%), followed by debenzylation with BCl_3 in DCM at 0 °C to provide the target alkaloid, (+)-lycoricidin **206** (55%) (Scheme 35).



Scheme 35: Synthesis of (+)-lycoricidine **206**.

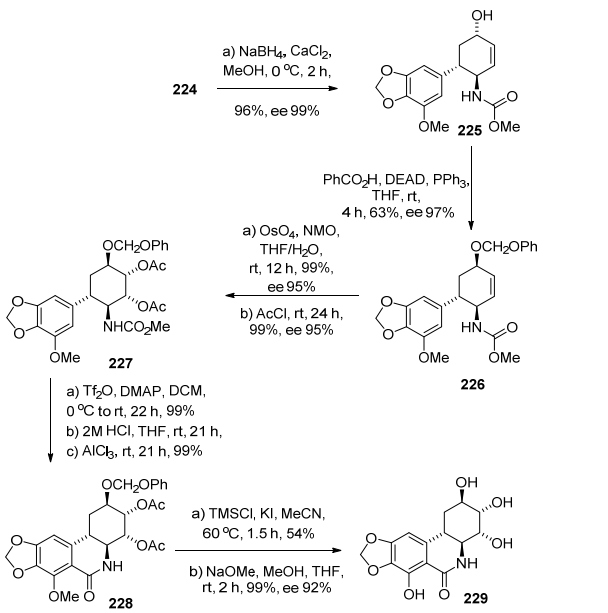
iv) Enantioselective total synthesis of (-)-*trans*-dihydronarciclasine, by Kádas and co-workers: Kádas and co-workers developed a feasible and reasonably inexpensive synthesis for the biologically active Amaryllidaceae isocarbostyril (-)-*trans*-dihydronarciclasine **229** [38]. Thus vanillin **215** was iodated with I_2 in an aqueous solution of KI and K_2CO_3 for 3 h to afford the desired 3-iodovanillin (99%), which was hydrolysed with aqueous NaOH in the presence of $CuSO_4$ to produce aldehyde **216** (64%). Treatment of **216** with CH_2Br_2 in DMF containing K_2CO_3 and CuO afforded myristicin aldehyde **217** (94%). The well-known Claisen-Schmidt condensation between **217** and acetone in aqueous NaOH then afforded the butenone **218** (67%). Michael addition between nitromethane and butanone **218** with a selected catalyst **219** gave the pivotal enantiomer (-)-**220** (57%, ee > 99%). The interesting Claisen-Henry condensation was then applied to **220** in order to generate the hydroxycyclohexanone **221** (38%), using ethyl formate as the carbon source. It was suggested that the reason a single enantiomer viz., (-)-**221** formed, could be ascribed to intramolecular

H-bonding between the adjacent 4-nitro and 3-hydroxy groups. Protection of the ketone group was facilitated by employing ethylene glycol and a catalytic amount of anhydrous oxalic acid in anhydrous MeCN to afford dioxolane (-)-**222** (90%). Reduction of the 4-nitro group was achieved using 10% Pd/C and H_2 at 80 °C, followed by chemoselective urethane formation on the amine group with methyl chloroformate to give (-)-**223** (95%, ee 95%). Release of the ketone at C1 with *p*-TsOH not only gave the expected ketone, but in addition, a dehydration in ring C occurred and afforded the enone (-)-**224** (99%, ee 98%) (Scheme 36).



Scheme 36: Synthesis of narciclasine precursor **224**.

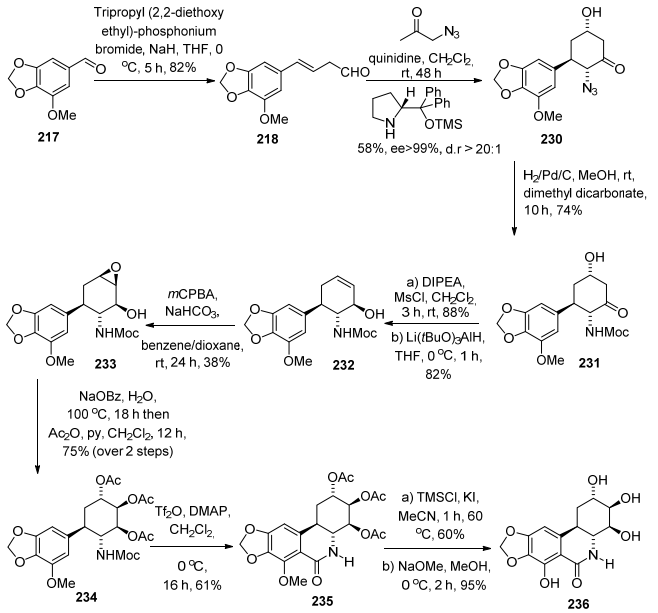
Utimoto's reduction of enone **224** afforded the stereoselective alcohol (-)-**225** due to axial attack of the hydride coordinated to the Ca^{2+} in 96% yield and ee 99%. It was necessary to invert the orientation of the C1 equatorial OH to the axial position. This was effected by a Mitsunobu protocol affording benzoate (-)-**226** (63%). A stereoselective Sharpless-Upjohn *cis*-dihydroxylation using



Scheme 37: Synthesis of (-)-*trans*-dihydronarciclasine **229**.

N-methylmorpholine *N*-oxide in the presence of OsO_4 gave the anticipated diol (99%), which was protected as its diacetate (-)-**227** (99%). Lactam formation was efficiently achieved via the Banwell modification of the Bischer-Napieralski protocol to afford an imine-methoxy intermediate, which upon acidic treatment produced lactam (-)-**228** (98% for 2 steps). Removal of the aromatic MeO group was effected with TMS-Cl in the presence of KI in MeCN (54%) and was followed by removal of the three acyl groups by NaOMe in THF to give (-)-**229** (99%, ee 92%) (Scheme 37).

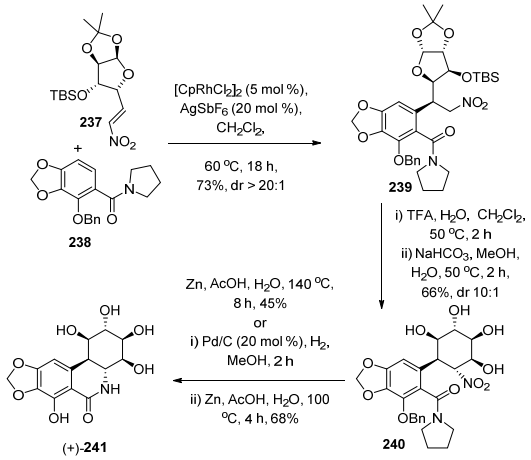
v) Total synthesis of (+)-*trans*-dihydronarciclasine via an asymmetric organocatalytic [3+3]-cycloaddition, by McNulty and co-workers: McNulty and co-workers developed an asymmetric synthesis of (+)-*trans*-dihydronarciclasine **236** employing an organocatalytic [3+3]-cycloaddition in an effective manner [39]. In this work, a two-carbon aldehyde homologation of the commercially available 5-methoxypiperonal **217** with a suitable Wittig reagent produced the alkenal **218** (82%), which was followed by the pivotal iminium ion-mediated [3+3]-Michael aldol reaction with the Jørgensen catalyst in combination with quinidine to afford the stereochemically desired chiral cycloadduct **230** (58% and ee>99%). Reduction of the azide in the presence of dimethyldicarbonate gave the Moc-protected compound **231** (74%). Dehydration of **231** was effected by mesylation of the OH in DIPEA for 3 h (88%) and was followed by reduction of the ketone to the equatorial alcohol **232** (82%) using Li(*t*BuO)$_3$AlH in THF at 0 °C. Epoxidation of the olefin proved problematic, but eventually *m*CPBA in benzene:dioxane (1:1) in the presence of $NaHCO_3$ afforded a 38% yield of the β-epoxide **233**. The epoxide ring was opened by treatment with sodium benzoate and immediately followed by protection as the triacetate **234** (75% for 2 steps). Generation of the phenanthridone ring was achieved using Banwell's modification of the Bischler-Napieralski reaction to give the tetracycle **235** (61%). The C7 MeO group was cleaved selectively, followed by removal of the three acetate protecting groups under basic conditions to finally afford (+)-*trans*-dihydronarciclasine **236** (Scheme 38).



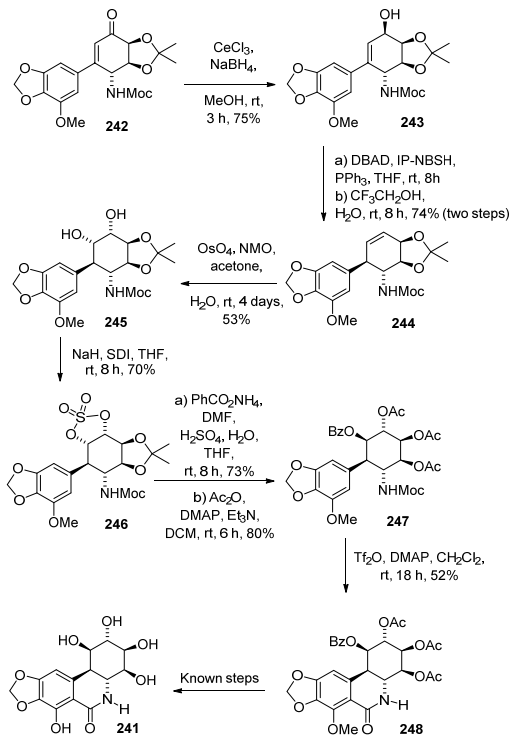
Scheme 38: Synthesis of (+)-*trans*-dihydronarciclasine **236.**

vi) Total synthesis of (+)-pancratistatin by the Rh(III)-catalyzed addition of a functionalized benzamide to a sugar-derived nitroalkene, by Potter and Ellman: Ellman and Potter developed

a remarkable diastereoselective Rh(III)-catalysed C-H bond insertion by a sugar-derived nitroalkene in their 10-step synthesis of (+)-pancratistatin **241** [40]. Their elegant synthesis commenced with the pivotal C-H bond insertion between nitroalkene **237** and amide **238** with a selected Rh(III) catalyst to afford the insertion product **239** (73%, dr >20:1) [41]. Removal of both the acetonide and silyl groups with aqueous TFA at 50 °C gave the crude furanose triol, which was immediately treated with aqueous $NaHCO_3$ in MeOH at 50 °C to afford the tetrahydroxy cyclohexane **240** (66%, dr 10:1). Treatment of this material with Zn/AcOH/H_2O at 140 °C in a sealed tube promoted reduction of the nitro group to afford (+)-pancratistatin **241** (45%). The authors suspected that H-bonding could facilitate the crucial transamidation steps and thus as an alternative, they firstly removed the benzyl group under Pd/C-catalysed hydrogenolysis to afford the corresponding phenol. When this compound was then subjected to Zn/AcOH reduction of the nitro group at 100 °C, (+)-pancratistatin **241** was produced in an improved yield of 68% (Scheme 39).



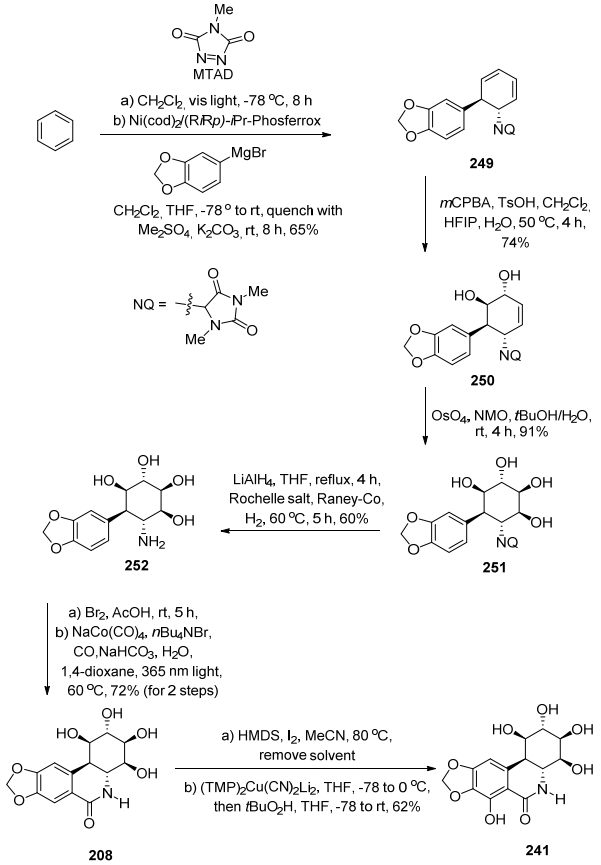
Scheme 39: Synthesis of (+)-pancratistatin **241**.



Scheme 40: New variation of the synthesis of (+)-pancratistatin **241** from an advanced intermediate **242**.

vii) Chemoenzymatic formal total synthesis of pancratistatin from narciclasine-type compounds via a Myers transposition, by Hudlicky and co-workers: Recently, Lapinskaite *et al.* published an improved synthesis of (+)-pancratistatin **241** starting from the relatively advanced intermediate **242** [42] which the group had synthesized earlier [43]. Luche reduction of enone **242** afforded the allylic alcohol **243** (75%). This was followed by a modified Myers' reductive transposition using di-*t*-butylazidodicarboxylate (DBAD) together with PPh_3 and 2-nitro-*N'*-(propan-2-ylidine)benzenesulfonohydroxide (IP-NBSH) which afforded the olefin **244** (64%). All attempts at *trans*-hydroxylation of the olefinic bond were unsuccessful and thus *cis*-hydroxylation via the Upjohn method with OsO_4 was carried out to provide the corresponding *cis*-diol **245** (53%). This was readily converted into the easier-to-handle sulfonate **246** (70%) by treatment with sulfonyldiimidazole (SDI) under basic conditions in THF. Treatment of the sulfonate **246** with ammonium benzoate afforded the desired *trans* triol (73%) by preferential *trans*-diaxial attack of the sulfonate **246**. After acidic work-up, the triol was converted into its triacetate analogue **247** (80%). Next the Banwell modification of the Bischler-Napieralski ring closure produced lactam **248** (52%), which could be transformed into (+)-pancratistatin **241** in two known steps (Scheme 40).

viii) Synthesis of (+)-pancratistatins via catalytic desymmetrization of benzene, by Sarlah and co-workers: Sarlah and co-workers developed a catalytic desymmetrization of benzene as a key starting point in their concise synthesis of (+)-pancratistatin **241** and (+)-7-deoxypancratistatin **253** [44]. The group applied an enantioselective dearomative *trans*-carboamination of benzene protocol to install the first two *vic* stereocentres employing MTAD as the nitrogen source coupled with the appropriate aryl Grignard reagent and using $Ni(cod)_2$ as catalyst for the synthesis of the



Scheme 41: Synthesis of (+)-7-deoxypancratistatin **208** and (+)-pancratistatin **241**.

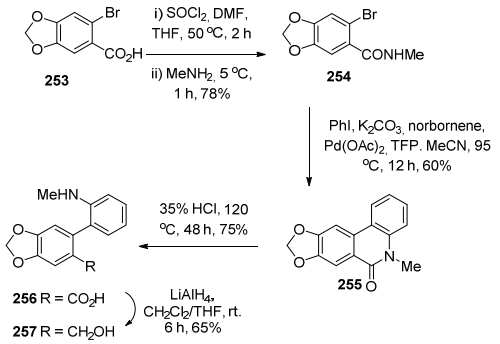
pivotal diene intermediate **249**, which was obtained on a 10 g scale. Chemoselective epoxidation of the more electron-rich distal alkene with *m*CPBA and subsequent stereoselective epoxide ring-opening with TsOH in a large excess of water containing hexafluoro-isopropanol (HFIP) afforded diol **250** (74%). An Upjohn dihydroxylation of the remaining alkene was effected with OsO_4 and NMO in *t*BuOH/H_2O at 22 °C to produce the important tetrol **251** as a single isomer in 91% yield. It should be noted that at this stage the original benzene ring had been fully functionalized into the pancratistatin core in which all the contiguous stereocentres had been installed.

Removal of the urazole protecting group with $LiAlH_4$ and Raney-Co under a H_2 atmosphere produced the free amine **252** (60%). Installation of the isocarbostyril framework was effected by initial bromination with Br_2/AcOH followed by $NaCo(CO)_4$-catalysed carbonylation under a CO atmosphere and UV irradiation and afforded (+)-7-deoxypancratistatin **208** (72% over two steps). In a new and novel C7 arene hydroxylation protocol the group developed, **208** was treated with HMDS and I_2 in MeCN at 80 °C followed by removal of solvent. The residue was then immediately treated with $(TMP)_2Cu(CN)_2Li_2$ in THF at -78 °C to effect C-7 cupration. Finally hydroxylation with *t*BuO_2H in THF at this 7 position completed the synthesis of (+)-pancratistatin **241** in a 62% yield (Scheme 41).

ix) Miscellaneous: Finally, in this section on pancratistatin syntheses, a paper describing the chemoenzymatic synthesis of triazololactams somewhat structurally related to pancratistatin, by de la Sovera *et al.* should be noted [45].

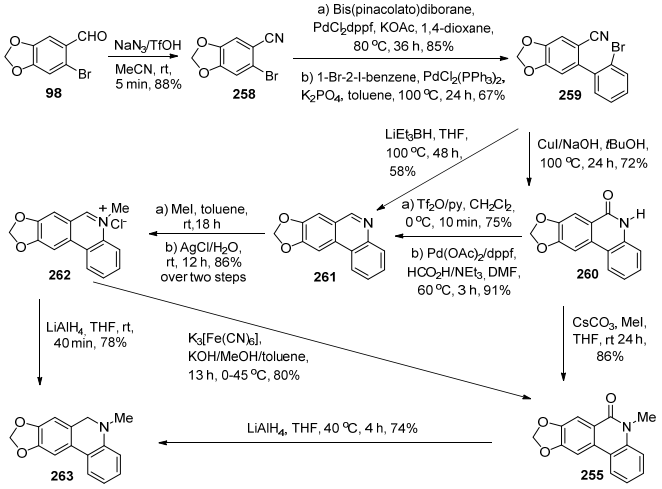
g) Phenanthridine-scaffold alkaloids

i) Synthesis of ismine, by Chen and co-workers: Chen and co-workers developed a short and efficient synthesis for the neuroprotective and antifungal Amaryllidaceae alkaloid ismine **257** starting from 2-bromo-4,5-(methylenedioxy) benzoic acid **253** [46]. Conversion to the acid chloride with $SOCl_2$, followed by treatment with methylamine afforded amide **254** (78%). Coupling between the latter bromo-amide **254** and iodobenzene using a palladium catalyst gave the new lactam **255** (60%). Acid hydrolysis of this lactam afforded the amino acid **256** (75%) which was subsequently reduced by $LiAlH_4$ to afford the desired ismine **257** (65%) (Scheme 42).



Scheme 42: Synthesis of ismine **257**.

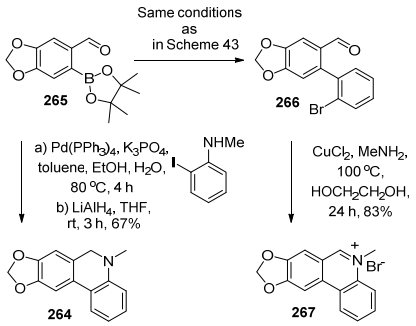
ii) Synthesis of phenanthridine skeletal alkaloids, by Fan-Chiang *et al.*: Fan-Chiang *et al*. developed a strategy which focused on the phenanthridine scaffold to develop a generalized synthetic protocol for a range of bicolorine type Amaryllidacae alkaloids [47]. For a recent review on this particular area, see the paper by Rafiee [48]. Thus, in the Fan-Chiang work, cyanation of commercially available bromo aldehyde **98** with sodium azide in CH_3CN containing TfOH afforded an 88% yield of bromo cyanide **258**. This compound was in turn converted into the corresponding boronic ester with bispinacolatodiborane in 85% yield, followed by a Suzuki coupling with 1-bromo-2-iodo benzene to form the pivotal biphenyl intermediate **259** in 67% yield. Cu-catalysed ring closure afforded crinasiadine **260** in 72% yield, which in turn proved to be a most useful general intermediate. Thus, treatment of **260** with Tf_2O in pyridine formed the iminotriflate, which upon hydrogenation with $Pd(OAc)_2$ and formic acid formed trisphaeridine **261** in 68% yield for the two steps. Finally, efficient methylation of **261** with MeI, coupled with an exchange of the I by Cl afforded bicolorine **262** in 86% yield (Scheme 43).



Scheme 43: Synthesis of bicolerine-type alkaloids.

Alternatively, methylation of crinasiadine **260** with MeI and Cs_2CO_3 in THF afforded *N*-methylcrinasiadine **255** (86%) and reduction of the latter with $LiAlH_4$ gave the corresponding 5,6-dihydrobicolotine **263** (74%). In order to reduce the number of steps for trisphaeridine **261**, biaryl **259** was treated with the super hydride, $Li(Et)_3BH$, which gave **261** in an albeit moderate yield of 58%, but nevertheless did save two steps starting with **98**. Further transformations included conversion of bicolorine **262** into either **263** by reduction with $LiAlH_4$ (78%), or **255** by oxidation with potassium ferricyanide (80%) (Scheme 43).

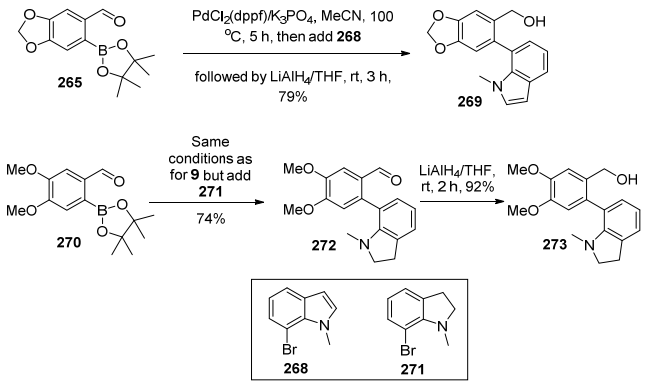
To shorten the overall number of steps even further, bromoaldehyde **98** was converted into the corresponding boronic ester **264** (95%) under the same Miyaura borylation conditions shown in scheme 43, followed by Suzuki coupling to afford aldehyde **265** (70%) for the two steps [49]. This was followed by the copper-catalysed annulation pioneered by the group to afford the bicolorine **266**



Scheme 44: Alternative routes to bicolorines.

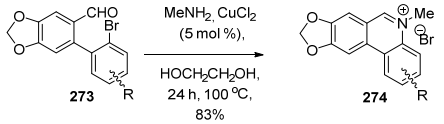
(83%) as the bromide salt, representing the shortest route to the bicolorine and its analogues to date. Finally 5,6-dihydrobicolorine **263** was prepared through Suzuki coupling between boronic ester **264** and *N*-methyl-2-iodoaniline, followed by $LiAlH_4$ reduction in a 67% yield for the two steps (Scheme 44).

The same authors then applied their proven strategies for the synthesis of three further indole alkaloids. Thus Suzuki coupling of boronic ester **264** with bromoindole **267**, followed by reduction with $LiAlH_4$ afforded galanthindole **268** (79%), while starting from the corresponding dimethoxy precursor **269**, followed by a Suzuki coupling with indole **270** afforded lycosinine B, **271** (74%). On reduction with $LiAlH_4$ this compound afforded lycosinine A, **272** (92%) (Scheme 45).



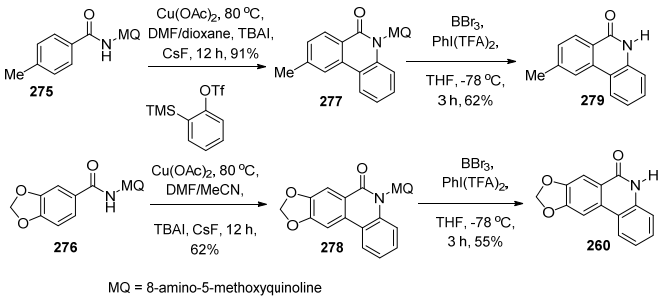
Scheme 45: Synthesis of galanthindole **268** and lycosinines A **272** and B **271**.

iii) Copper-catalyzed annulation for the synthesis of phenanthridinium bromides, by Jiang *et al.*: Jiang *et al.* in realizing that an efficient and scalable protocol for the synthesis of *N*-substituted phenanthridine alkaloids found in Amaryllidaceae plants was lacking to support phamaceutical research efforts, considered a Cu-catalyzed C-N bond formation coupled with a ring closure protocol as an option [49]. The group developed one of the shortest routes to the bicolorine Amaryllidaceae alkaloids. Thus treatment of the general diaryl system **273** with methyl amine in the presence of 5 mol % $CuCl_2$ in ethylene glycol at 100 °C for 24 h afforded bicolorine **274** (83%, R = H) (Scheme 46). By suitably substituting the bromo aryl ring in the starting material, i.e. the R group, a range of different bicolorines were readily synthesized.



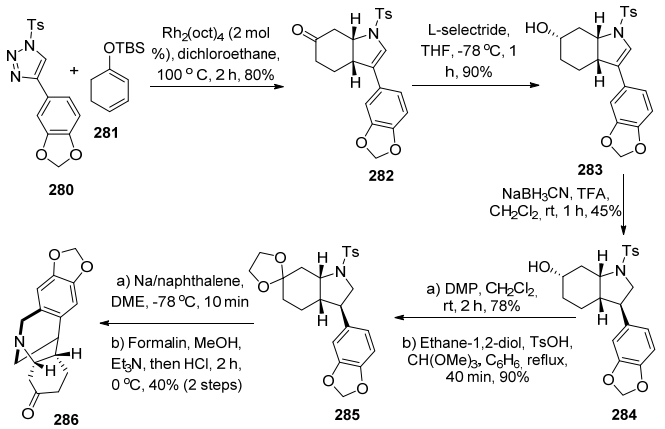
Scheme 46: General synthetic strategy of bicolorines **274**.

iv) Copper-catalyzed selective *ortho*-C-H/N-H annulation of benzamides with arynes for the synthesis of phenanthridinone alkaloids, by Zhang *et al.*: Zhang *et al.* also interrogated application of copper-catalysed annulation protocols in their rendition of the synthesis of the phenanthridinone Amaryllidaceae alkaloids [50]. Their protocol involved a selective *ortho*-C-H/N-H annulation. Thus treatment of the amides **275** and **276** with benzyne generated from the Kobayashi benzyne pecursor shown in Scheme 47 in the presence of $Cu(OAc)_2$, CsF and TBAI in O_2 at 80°C, afforded the respective *N*-protected amides **277** (91%) and **278** (62%) respectively. Simple removal of the nitrogen-protecting group with BBr_3 and $PhI(TFA)_2$ produced phenaglydon **279** (62%) and crinasiadine **260** (55%), representing a short and efficient synthetic protocol for these scaffolds (Scheme 47).



Scheme 47: Synthesis of phenaglydon **279** and crinasiadine **260**.

v) Rhodium-catalyzed denitrogenative [3+2] cycloaddition providing access to functionalized hydroindolones and the framework of montanine-type alkaloids, by Zhai and co-workers: Zhai and co-workers developed a Rh(II)-catalysed denitrogenative [3+2] cycloaddition protocol to successfully gain rapid entry into the montanine-type Amaryllidaceae alkaloid scaffold [51]. Thus reaction between the sulfonyl-1,2,3-triazole **280** with the cyclic dienol TBS ether **281** in the presence of $Rh_2(oct)_4$ in dichloroethane at 100 °C for 2 h afforded the aza-[3+2] cycloadduct **282** (80%) (Scheme 48).

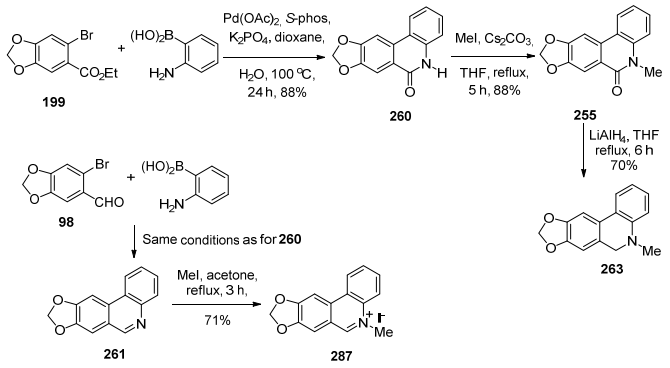


Scheme 48: Synthesis of 5,11-methanomorphanthridin-3-one **286**.

Reduction of the ketone moiety with L-selectride in THF at -78 °C gave alcohol **283** (90%), which was followed by a poor yielding reduction of the double bond of the pyrrole ring by $NaBH_3CN$ to yield the *trans*-octahydroindolone **284** (45%). Oxidation of the secondary alcohol with DMP (78%) was followed by its protection as the ketal **285** (90%). The Ts group was then removed by sodium naphthalide at -78 °C, followed by a Pictet-Spengler cyclisation with formalin to produce the all-important 5,11-methanomorphanthridine-3-one **286** (40% for the two steps), which represents the basic scaffold of the montanine alkaloids (Scheme 48).

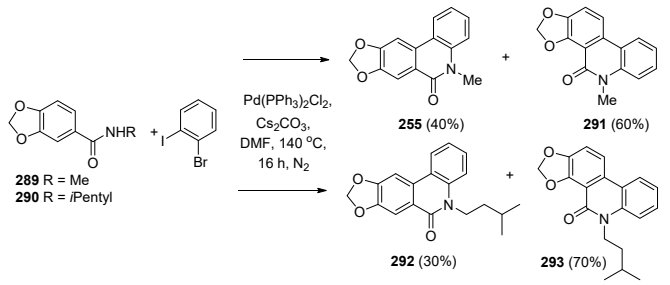
vi) Synthesis of phenanthridinone alkaloids via Suzuki-Miyaura cross-coupling, by Tanimori and co-workers: Tanimori and co-workers extended their developed protocol for the synthesis of some new phenanthridone alkaloids via Suzuki-Miyaura cross-coupling in the following way [52]. Reaction between ester **199** and 2-aminobenzeneboronic acid catalysed by $Pd(OAc)_2$, (*S*)-phos and K_2PO_4 in 1,4-dioxane/H_2O at 100 °C for 24 h afforded the Amaryllidaceae alkaloid crinisiadine **260** (88%) in a single step which was converted into *N*-methyl crinasiadine **255** (88%) by treatment with MeI/$CsCO_3$ in THF under reflux. Reduction of lactam **255** with $LAlH_4$/THF under reflux afforded 5,6-dihydrobicolorine **263** (70%). On the other hand, reaction between

the same boronic acid under the same conditions as for **260**, but with aldehyde **98** afforded trisphaeidine **261** (50%) which when subjected to methylation with MeI/acetone under reflux provided bicolorine **287** (71%) (Scheme 49).



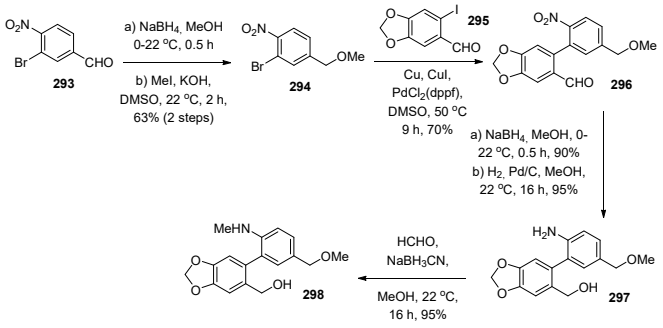
Scheme 49: Synthesis of crinasiadine **260** and bicolorines **263** and **287.**

vii) Palladium-catalyzed direct synthesis of phenanthridones from benzamides through tandem N-H/C-H arylation, by Banerji and co-workers: The group of Banerji and co-workers developed a new synthetic protocol for construction of phenanthridones related to the Amaryllidaceae alkaloids requiring no directing group nor external ligand to assist in the reaction [53]. Their protocol involved condensation between the easily accessed benzamides **288** and **289** with 1-bromo-2-iodobenzene in a sealed tube in the presence of $Pd(PPh_3)Cl_2$ as catalyst and $CsCO_3$ in DMF at 140 °C/N_2 for 16 h. It is clear in this instance, that the intermolecular C-C and C-N bond formation to form the corresponding regioisomeric phenanthidones **255** and **290**, as well as **291** and **292** occurred in a single step. This protocol, not only represents an amazingly short and easy route for the two Amaryllidaceae alkaloids **255** and **291**, but also establishes an intriguingly new class of phenanthridone alkaloids viz., **290** and **292**, in good yield (Scheme 50)



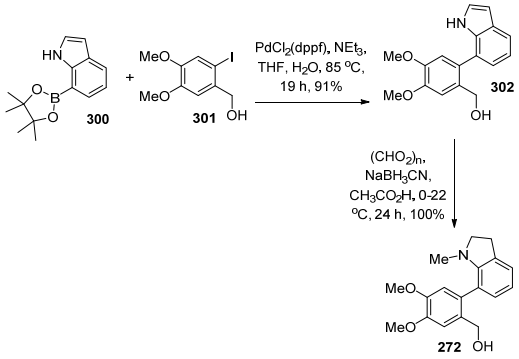
Scheme 50: Synthesis of *N*-methylcrinasiadine **255** and *N*-isopentyl-crinasiadine **291**.

viii) Total syntheses of zephycandidine III and lycosinine A, by Banwell and co-workers: Banwell and co-workers, after failing to form the important aryl-aryl bond between two relevant precursors for their synthesis of the two Amaryllidacea alkaloids zephycandidine III, **298** and lycosinine A **272** via the anticipated Suzuki-Miyaura cross coupling protocol, resorted to the palladium-catalysed Ullmann cross coupling which proved more successful [54]. Thus reduction of aldehyde **293** with sodium borohydride and methylation of the resulting primary alcohol with methyl iodide in DMSO containing KOH, afforded methyl ether **294** (63% for the two steps). Palladium-catalysed Ullmann cross coupling with aldehyde **295** then afforded the pivotal biaryl compound **296** (70%). Reduction of the aldehyde moiety with sodium borohydride in MeOH was followed by reduction of the nitro group under catalytic hydrogenolysis to afford the amino alcohol **297** (86% for the 2 steps). In order to methylate the primary amine of **297** in the presence of the primary benzylic alcohol moiety, a reductive monomethylation was efficiently performed using a molar equivalent of formaldehyde in the presence of sodium cyanoborohydride to provide zephycandidine **298** (95%) (Scheme 51).



Scheme 51: Synthesis of zephycandidine **298**.

Lycosinine A **302**, on the other hand, was prepared by the Suzuki-Miyaura cross coupling protocol. Thus the C7 borylated indole **299** was successfully cross coupled with aryl iodide **300** in the presence of $PdCl_2$(dppf) to afford the biaryl compound **301** (91%). A most interesting reductive methylation of indole **301** using paraformaldelyde and sodium cyanoborohydride was effected. Not only was the indole *N*-methylated, the 5-membered ring of the indoline was also reduced to afford lycosinine A **272** (100%) (Scheme 52).



Scheme 52: Synthesis of lycosinine A **272**.

h) Plicamine-scaffold alkaloids

i) Multicomponent access to indolo 3,3a-c-isoquinolin-3,6-diones as a formal synthesis of (±)-plicamine, by Mijangos and Miranda: (±) Plicamine **303** is a rather novel example of a tetracyclic indolo[3,3a-*c*]isoquinoline scaffold which forms the identifying motif common to the plicamine alkaloids found in many Amaryllidaceae alkaloid families. A multistep solid support synthesis by Ley and co-workers afforded (+)-plicamine **303** (Figure 4) [55-57].

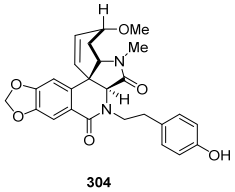
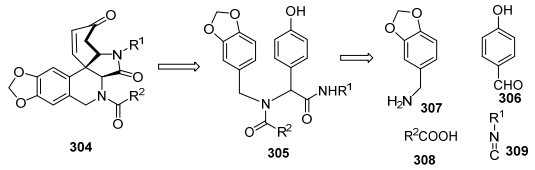


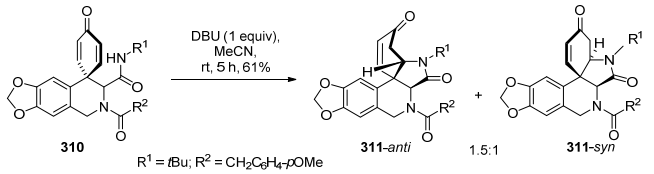
Figure 4: (+)-Plicamine **303**.

Some 10 years later, Mijangos and Miranda developed the Ugi-4CR in their shortened protocol to successfully construct the core indolo[3,3a-*c*]isoquinolinone nucleus in an innovative way [58]. In their retrosynthetic analysis, they reasoned that the core nucleus **304** could be derived from the precursor **305**, which in turn could be derived from an Ugi-4CR protocol between *p*-hydroxybenzaldehyde **306**, piperonyl amine **307**, a carboxylic acid **308** and an isocyanide **309** illustrated in Retrosynthetic Scheme 53.



Scheme 53: Retrosynthetic analysis incorporating the Ugi-4CR for the indoloisoquinoline core.

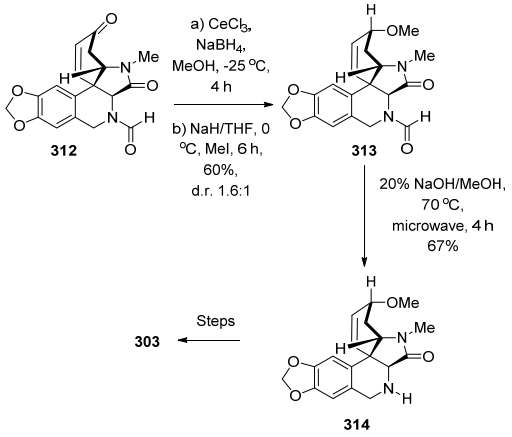
The proposed route incorporates the possibility of producing a number of analogues since various acids **308** and isocyanates **309** can be incorporated. Thus, optimum conditions derived by the group involved initial reaction between aldehyde **306** and amine **307** to pre-form the corresponding imine after which the respective isocyanide and carboxylic acid were added, followed by heating the resultant mixture in MeOH under microwave conditions at 60 °C. In this way good yields of **305** (for example R^1 = *t*Bu; R^2 = $CH_2C_6H_4$-*p*OMe, 80%) were obtained. The next step in the synthesis involved an intramolecular oxidative de-aromatization phenolic coupling protocol which was most efficiently accomplished by treatment of intermediates **305** with phenyliodine(III)bistrifluoroacetate) (PIFA) in 2,2,2-trifluoroethanol (2,2,2-TFE) at -25 °C. Cyclisation was rapid and almost quantitative to produce the spirodienone intermediates **310**, which had to be immediately isolated due to their instability at low pH (Scheme 54).



Scheme 54: Aza-Michael products **311**-*anti* and **311**-*syn* of spiridienone **310**.

In order for the 5-membered lactam ring to be formed for the core indoloisoquinoline scaffold, an intramolecular aza-Michael condensation was required and the quaternary spirocyclic system adjacent to the free rotating amide R^1NH supported this. Thus treatment of **310** (R^1 = *t*Bu, R^2 = $CH_2C_6H_4OMe$) with l eqivalent of DBU in MeCN at 22 °C for 5 h afforded a 61% yield of **311** (*anti*: *syn* = 1.5 : 1.0). In order to improve both the yield and selectivity of the protocol, it was found that removal of the solvent following the phenolic coupling of **305** should be followed by the immediate addition of 4 eqivalents of DBU in MeCN in a one-pot sequence, which then afforded **311** in a 56% yield.

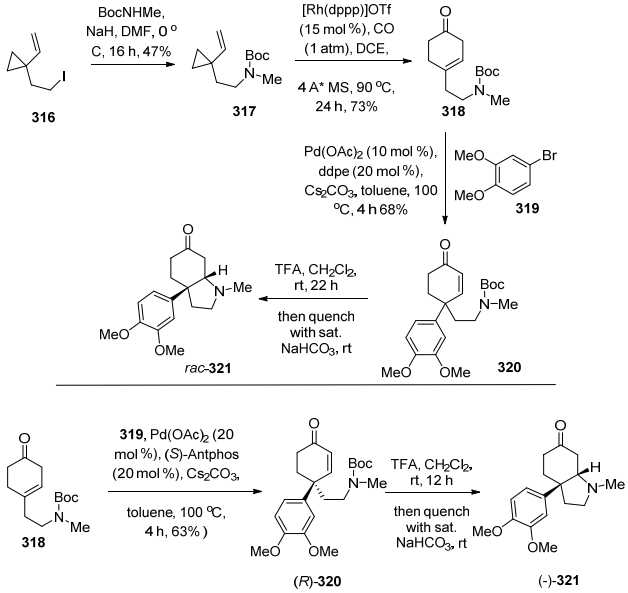
Finally, the conjugated ketone functional group of precursor **312** (as an example) was chemoselectivly reduced under Luche conditions followed by treatment of the crude product with NaH in THF at 0 °C and then with MeI to afford a 60% yield of the *endo* methyl ethers **313** (d.r. 1.6:1). Fortunately, the desired stereoisomer was the major product formed. Deformylation with methanolic NaOH in a microwave oven promoted hydrolysis at 70°C and gave a 67% yield of the serendipitous thermodynamically favoured diastereomer **314** (d.r. 30:1), which upon alkylation and oxidation to the lactam using conditions developed by Ley and co-workers can be converted into (±)-plicamine **303** (Scheme 55).



Scheme 55: Conversion of precursor **312** into *rac*-plicamine **303**.

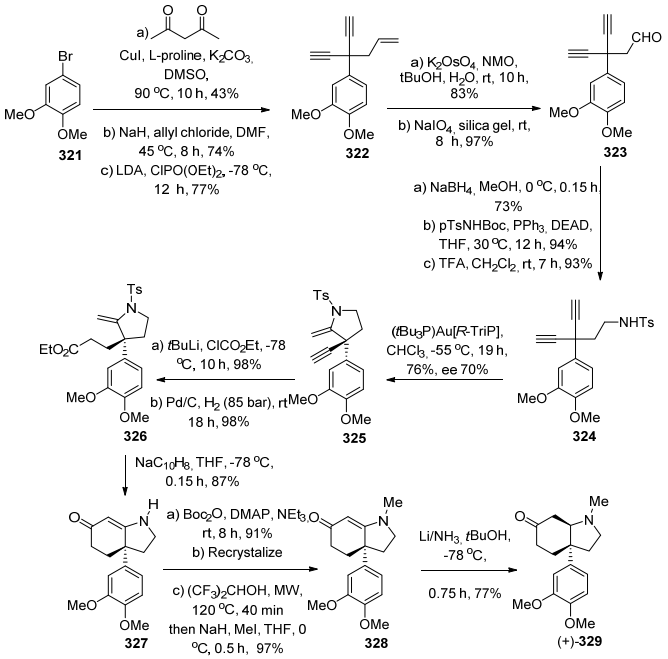
i) Mesembrine-scaffold alkaloids

i) Total synthesis of (-)-mesembrine, by Yu and co-workers: Yu and co-workers developed a most efficient synthesis of the Amaryllidaceae alkaloid mesembrine *rac*-**320** by making use of a [5+1] cycloaddition and an (*S*)-Antphos ligand-palladium catalysed Buchwald coupling strategy [59]. For a recent review on this particular alkaloid, see the paper authored by Krstenansky [60]. The Yu synthesis started by an S_N2 displacement of the iodine in **315** by a BocNHMe moiety to afford the corresponding *N*-Boc analogue **316** (47%).This was followed by the [5+1] cycloaddition protocol involving ring-opening of the cyclopropane by the Rh(I) catalyst to form a transient intermediate which when exposed to CO gas afforded the cyclohexenone **317** (73%). Next the Buchwald coupling between the enone **317** with 0.7 equiv of bromoaryl **319** afforded racemic **319** (68%) with the installation of the all-important quaternary centre being accomplished. Racemic mesembrine **320** was then obtained by treatment of **319** with TFA to remove the Boc and facilitated the intramolecular aza-Michael ring closure in 76% yield. The authors found that by employing Tang's (*S*)-Antphos ligand (20 mol %) in conjunction with $Pd(OAc)_2$ (20 mol %) for the critical Buchwald coupling, they were successful in isolating a 63% yield of chirally pure **319**, which upon removal of the Boc group with TFA afforded (-)-mesembrine **320** (73%, ee 86%) (Scheme 56).



Scheme 56: Synthesis of (-)-mesembrine **320**.

ii) Total synthesis of (+)-mesembrine by the application of asymmetric gold catalysis, by Czekelius and co-workers: Czekelius and co-workers used an asymmetric gold catalyst in their synthesis of (+)-mesembrine [61]. Their synthesis commenced with the commercially available 4-bromoveratrole **321** which was subjected to an Ullmann cross-coupling reaction with acetylacetone in the presence of CuI as catalyst to afford the expected diketone (43%). This compound was then allylated at the benzylic carbon (74%) and finally transformed into the 1,4-diyne **322** (77%) via the corresponding enol phosphate ester following an adaptation of the Negishi protocol. Chemoselective dihydroxylation (83%) using the Upjohn protocol at the alkene moiety followed by glycol oxidation with $NaIO_4$ on silica gel gave the 1,4-diyne aldehyde **323** (97%). Reduction of the aldehyde with $NaBH_4$ afforded the expected primary alcohol (73%), which was followed by a Mitsunobu-type reaction with Boc-*p*-tosylamide, and by an acid-mediated deprotection of the Boc group to afford the tosyl diyne **324** (87% for the 2 steps). The gold-catalysed enantioselective desymmetrization cyclo-isomerisation protocol developed by the authors was next applied to the tosyl diyne **324** to afford the methylene pyrrolidine **325** (76%, ee 76%). Conversion of pyrrolidine **325** into the acetilide by *t*BuLi, followed by treatment with ethyl chloroformate and chemoselective hydrogenation afforded pyrrolidine **326** (97% for the 2 steps). Removal of the Ts protecting group with sodium naphthalenide lead to the formation of the indole skeleton **327** (97%). At this vital stage, it was necessary to Boc-protect the vinylogous indole **327** in order to recrystallize it from hexane/Et_2O, which increased the ee > 99%. This compound was then transformed into the *N*-methyl intermediate **328** (97%), before final conjugate alkene reduction with Li/NH_3 to give (+)-mesembrine **329** (77%) (Scheme 57).



Scheme 57: Synthesis of (+)-mesembrine **329**.

j) Minor scaffolds

i) Biomimetric total synthesis of the pentacyclic alkaloid derivative Graciliamine by Gao, Banwell and Willis: Gracilamine **(**Figure 5) **345** is an intricately structured pentacyclic Amaryllidaceae alkaloid isolated from *Galanthus* gracilis from Turkey and has had its structure confirmed by single crystal x-ray analysis [62].

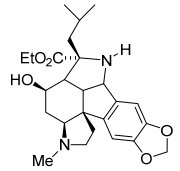
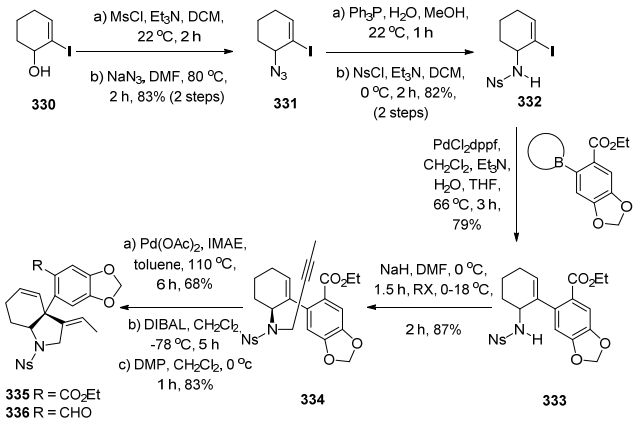


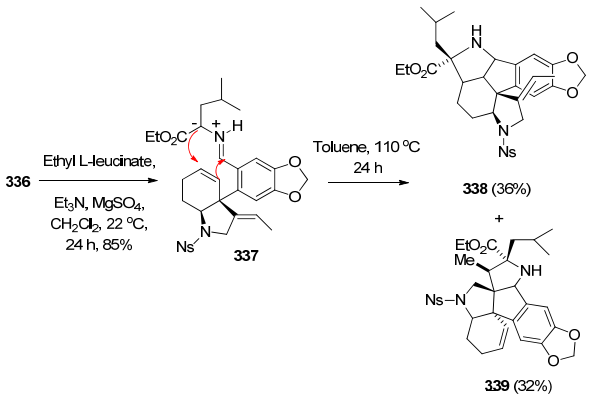
Figure 5: *rac*- Gracilamine **345**.

Banwell and co-workers commenced their synthesis by mesylation of the readily available iodocyclohexene **330** employing the Crossland-Servis protocol to form the corresponding mesylate, which was then treated with sodium azide in DMF to afford iodoazide **331** (83% for the 2 steps) [63]. The latter azide **331** was reduced under Staundinger conditions to the amine, which was then protected as the nosyl amine **332** (82% for 2 steps). Suzuki-Miyaura cross-coupling with the respective aryl borate afforded the aryl cyclohexene intermediate **333** (79%) (Scheme 58).



Scheme 58: Synthesis of hexahydroindole aldehyde **336**.

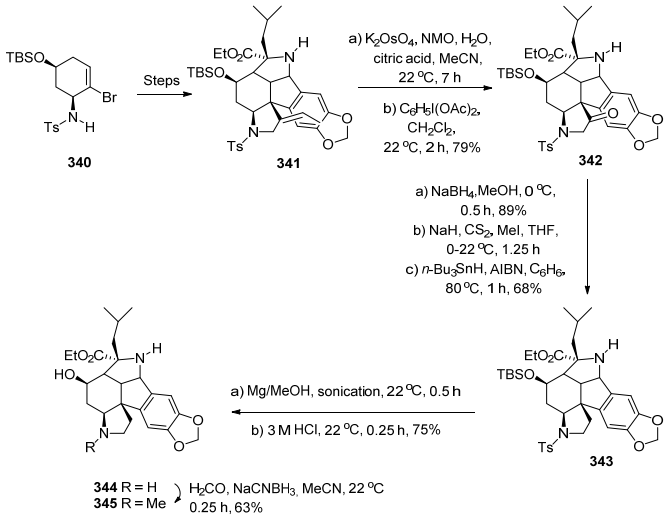
Removal of the N-H proton of **333** with NaH followed by reaction with 1-bromo-2-butyne (RX in scheme 58) produced the corresponding 1,6-enyne **334** (87%). Heating the latter compound in toluene containing $Pd(OAc)_2$ resulted in an intramolecular Alder-ene (IMAE) cyclisation to produce the hexahydroindole **335** (68%). Reduction of the ester group of **335** to the corresponding alcohol, accomplished with DIBAL-H, was followed by Dess-Martin oxidation to afford aldehyde **336** (83%)(Scheme 58). The crucial proof of concept was then undertaken by reaction of aldehyde **336** with ethyl L-leucinate in trimethylamine and $MgSO_4$ at 22 °C to generate the pivotal transitional azomethine ylide **337**. This compound was perfectly set up for the thermal [3+2] cycloaddition which was accomplished by heating it in toluene under reflux for



Scheme 59: Proof of concept for the [3+2] cycloaddition.

24 h to afford the desired product **338** (36%), together with the inevitable alternative **339** (32%), due to reaction with the exocyclic olefin residue (Scheme 59).

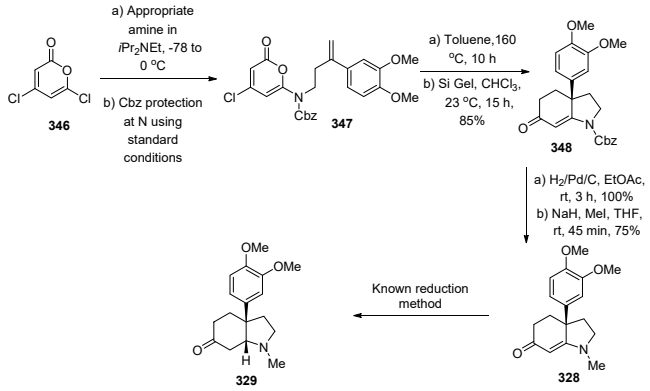
In order for the β-OH group to be introduced into ring E of gracilamine **345**, the allylic amine **340** was treated via a similar protocol as illustrated in Schemes 58 and 59 to produce the corresponding analogue **341**. Removal of the exocyclic olefinic group was achieved in 3 major steps. Firstly, the exocyclic olefin group was dihydroxylated with OsO_4 and then oxidized to the corresponding ketone **342** with iodobenzene diacetate (79% for the two steps). Secondly, reduction of the ketone with sodium borohydride in methanol afforded the corresponding β-OH alcohol (89%) which was converted into its xanthate and thirdly this compound was treated under the Barton-McCombie protocol for deoxygenation using tri-*n*-butyltin hydride to afford the required perhydroindole **343** (68%). Removal of the Ts group on the nitrogen atom was accomplished by treatment with magnesium in MeOH and the resulting amine was then treated with 3 M HCl to cleave the TBS ether to afford the amino alcohol **344** (75% for the 2 steps). Finally, an Eschweiler-Clark reductive amination, using formaldehyde and sodium cyanoborohydride, produced (±) gracilamine **345** (63%) (Scheme 60).



Scheme 60: Synthesis of *rac*-gracilamine **345**.

ii) Pyrone Diels-Alder routes to indolines and hydroindolines resulting in the syntheses of gracilamine, mesembrine, and Δ^7-mesembrenone, by Snyder and co-workers: Snyder and co-workers developed an expeditious protocol they described as a "pyrone Diels-Alder route" to gracilamine, mesembrine and Δ^7-mesembrenone [64]. This group also wished to develop key building blocks for the general synthesis of Amaryllidaceae alkaloids. To this end, they developed a protocol from a single starting material viz., 4,6-dichloropyrone **346**.

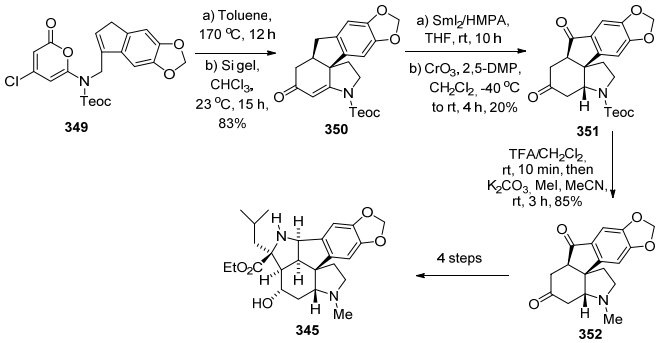
Thus, treatment of pyrone **346** with the appropriate amine, displaced the 6-chloro group and was followed by carbobenzyloxy protection of the amine under standard conditions to produce pyranone **347** with a tethered olefin at the 3'-position. The aromatic moiety at the 3'-position can also be changed to the 3,4-OCH_2O-group as well. Pyranone **347** was heated under microwave conditions in toluene to 160°C for 10 h to afford the Diels-Alder adduct which was gratifyingly found to undergo hydrolysis of the vinylogous chloride during silica gel chromatography to afford enone **348** (85%). Removal of the Cbz group was effected by



Scheme 61: The pyrone Diels-Alder approach to the mesembrines.

reduction using H_2/Pd/C and followed by methylation with NaH and MeI to yield Δ^7-mesembranone **328** (75% for the 2 steps). Finally, application of known reduction methodology to the conjugated enone of **328** afforded (±) mesembrine **329** (Scheme 61).

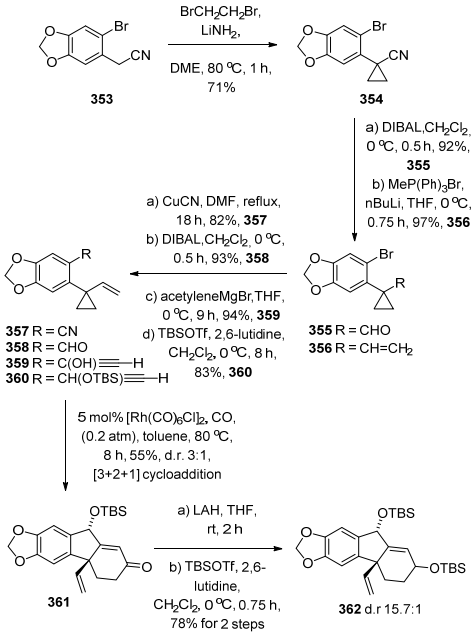
The group then embarked on a shorter route for the preparation of gracilamine **345** in which pyrone **349** was the starting material prepared in six steps. Microwave heating of pyrone **349** at 170 °C for 12 h facilitated the pyrone Diels-Alder cascade reaction to afford, after treatment on a silica gel column to effect hydrolysis of the vinylous chloride, the enaminone **350** in an amazing 83% yield. After some trial and error it was found that the most efficient way to reduce the olefinic bond was treatment of **350** with SmI_2 activated with HMPA in THF at 23 °C for 10 h to afford the corresponding alcohol, together with reduction of the double bond, as a single unassigned diasteresoner of the C-OH bond but with the correct ring junction configuration. Oxidation of the alcohol using the Salmond protocol effected oxidation of both the alcohol function as well as the benzylic group of the 5-membered ring to give diketone **351** in an overall yield of 20% from **350**. Removal of the Teoc group was effected by treatment with TFA and subsequent methylation with MeI and K_2CO_3 afforded the corresponding methyl diketone **352** (85% for the 2 steps). Since other workers had earlier converted diketone **352** into gracilamine **345** in 4 further steps, this synthesis requires only 10 steps from commercially available starting materials (Scheme 62).



Scheme 62: Synthesis of *rac*-gracilamine **345**.

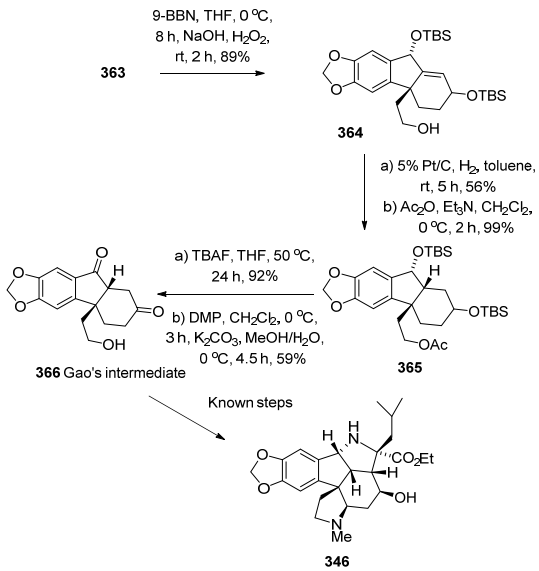
iii) Formal synthesis of graciliamine using a Rh(I)-catalysed [3+2+1] cycloaddition, by Bose, Yang and Yu: Yu and co-workers employed an intriguing Rh(I)-catalyzed [3+2+1] cycloaddition protocol in a new formal synthesis of the Amaryllidaceae alkaloid gracilamine [65]. Starting from bromide **353**, treatment with 1,2 dibromoethane and lithium amide in DME

produced the cyclopronane **354** (71%), which in turn was treated with DIBAL to give the corresponding aldehyde **355** (92%). A Wittig reaction with methylene triphenyl phosphorane afforded the alkene **356** (97%). Heating the latter alkene **356** with CuCN in DMF under reflux for 18 h gave the corresponding cyano alkene **357** (82%), which was hydrolysed with DIBAL to the aldehyde **358** (93%) and then subjected to a further Grignard reaction with ethynyl magnesium bromide to produce alcohol **359** (94%), which was protected as its OTBS ether **360** (83%). Next followed the pivotal Rh(I)-catalysed [3+2+1] cycloaddition protocol with CO at 80 °C and using a 5 mol % catalytic loading which afforded the *trans* tetracyclic ketone **361** (55%) after chromatographic separation from the *cis* diastereomer. LAH reduction of the ketone moiety to the alcohol, followed by protection with TBSOTf gave **362** (78% ever 2 steps) with a d.r. = 15.7:1 (Scheme 63).



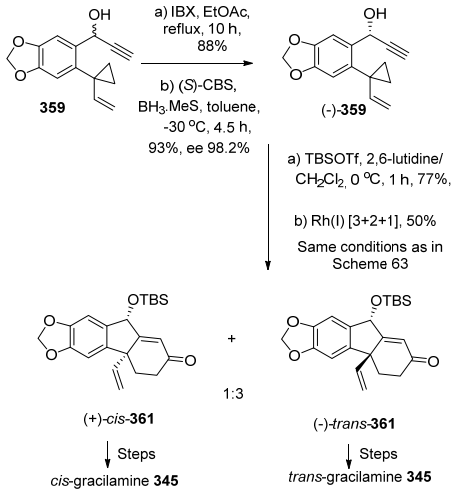
Scheme 63: Synthesis of intermediate **362**.

Subsequent hydroboration-oxidation of the vinylic double bond of **362** with 9-BBN afforded primary alcohol, **363** (98%). Catalytic hydrogenation with H_2 on 5% Pt/C in toluene reduced the ring–junction double bond to give the *syn* product (56%) (structure not illustrated), which was followed by acetylation of the primary alcohol to afford acetate **364** (99%). This was subsequently treated with TBAF to chemoselectively remove the TBS protecting groups and both secondary alcohol groups were oxidized to the corresponding ketones with Dess-Martin periodane. Finally, removal of the acetate protecting group afforded the diketo-alcohol **365** (59% for the 2 steps) known as Gao's intermediate. This was finally converted by known methodology into gracilamine **345** and thus represents a new formal synthesis of this novel pentacyclic biologically active alkaloid (Scheme 64).



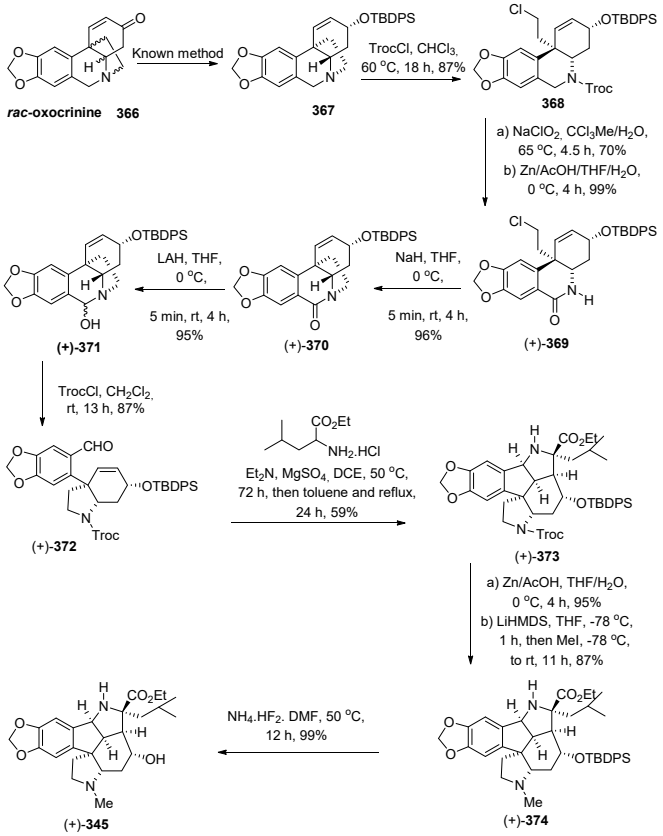
Scheme 64: Formal synthesis of gracilamine **345**.

On the other hand, the authors' asymmetric synthesis of gracilamine **345** commenced by oxidation of the previously synthesized alcohol **359** into the corresponding ketone in refluxing ethyl acetate containing IBX, after which the latter ketone was reduced with the (*S*)-CBS reagent and $BH_3.Me_2S$ to give the chiral propargyl alcohol (-)-**359** with ee 98.2%. Employing essentially similar synthetic protocols, both the *cis* and *trans* isomers of gracilamine **345** were synthesized (Scheme 65).



Scheme 65: Synthesis of chiral *cis*- and *trans*-gracilamine **345**.

iv) Asymmetric total synthesis of gracilamine, by Zhou and co-workers: Zhou and co-workers very recently reported on a biomimetically based synthetic protocol for the first asymmetric total delivery of (+)-graciliamine **345** from the known *rac*-oxocrinine **366** [66]. Asymmetric hydrogenation of *rac*-oxocrinine **366** by a known procedure and protection of the resulting alcohol as the TBDPS protected (+)-epivittatine **367** (43%, 93% ee) was accomplished on a gram scale (Scheme 66). Next the (+)-epivittamine **367** was ring-opened by treatment with TrocCl and $CHCl_3$ at 60°C for 3 h to afford (+)-**368** (87%) on a 4 g scale. Benzylic oxidation was effected with $NaClO_2$ in trichloroethene/H_2O at 65°C for 4.5 h to produce the (+)-lactam (70%) (not illustrated) on a 5 g scale. Removal of the Troc group with Zn/AcOH at 0°C afforded the corresponding deprotected (+)-lactam **369** (99%) on a 3 g scale. Treatment of this lactam with NaH to remove the H from the N-H group then facilitated the intramolecular cyclisation to produce the pentacycle **370** (96%) on a 2 g scale which was then carefully reduced with $LiAlH_4$ in THF at 0°C to produce a 4:1 mixture of the diastereomeric alcohols **371** (95%) on a 2.4 g scale. The lactol ring was then opened by treatment with TrocCl in DCM at 22°C to produce the most important intermediate viz., (+)-**372** (87%) on a 2.3 g scale.



Scheme 66: Asymmetric synthesis of (+)-gracilamine **345** from rac-oxocrinine **366**.

Condensation between (+)-benzaldehyde **372** and leucine ethyl ester hydrochloride, followed by an intramolecular [3+2] cycloaddition of the resulting imine (similar to Ma's protocol) [62] afforded the hexacyclic ester (+)-**373** (59%) on a 1.3 g scale and as a single isomer. Removal of the Troc group was effected with Zn/AcOH and followed by chemoselective methylation of the one pyrrolidine N-atom with LiHMDS and MeI in THF at -78°C to produce the hexacycle (+)-**374** (83%) for the two steps on a scale of 0.7-0.9 g. Finally, removal of the TBDPS protecting group with $NH_4.HF_2$ in DMF at 50°C for 12 h produced (+)-gracilamine **345** (99%) on a 0.6 g scale to complete the synthesis in an overall 9.9% yield in 11 steps from *rac*-oxocrinine **366** (Scheme 66).

Conclusions: The numerous new papers published in the very recent past (mid 2016 to 2017) dealing with syntheses of Amaryllidaceae alkaloids attests to the real value that these alkaloids possess as biological scaffolds and upon which many new ventures into their use in addressing medical conditions faced in all countries of the world will be conducted. Some groups have furthermore developed scaled up protocols in order to deliver the alkaloids on a gram scale for further in-depth evaluations in order to broaden the scope of evaluation and one cannot fail to wonder what these intriguing alkaloids might one day become famous for. It is also of note that the challenging structures of some of the alkaloids continue to attract the attention of synthetic chemists and will thus continue to foster developments in the area of new synthetic methods. Most of the general scaffold motifs had a reasonable number of syntheses (1-4 papers per topic), while the crinine and galanthamine scaffolds saw slightly more research interest (5-6 manuscripts). The phenanthridine and phenanthridone scaffold-based investigations remain very popular with 8 papers on each. It was also very clear that the structural complexity of gracilamine has captured the imagination of a number of research groups and four impressive investigations on the synthesis of this alkaloid were detailed during the 18 month period of the review. It was also noted that relatively few biomimetic protocols have been published during the period of the review and those that have, seem to point to perhaps the future routes which might yet prove to be the most fruitful.

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